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(54) Title: NUCLEIC-ACID BINDING PROTEINS

(57) Abstract

The invention provides human nucleic-acid binding proteins (NuABP) and polynucleotides which identify and encode NuABP. The invention also provides expression vectors, host cells, antibodies, agonists, and antagonists. The invention also provides methods for diagnosing, treating, or preventing disorders associated with expression of NuABP.

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NUCLEIC-ACID BINDING PROTEINS

TECHNICAL FIELD

This invention relates to nucleic acid and amino acid sequences of nucleic-acid binding proteins and to the use of these sequences in the diagnosis, treatment, and prevention of reproductive, immune, and neurological disorders, and cell proliferative disorders including cancer.

BACKGROUND OF THE INVENTION

Multicellular organisms are comprised of diverse cell types that differ dramatically both in structure and function. The identity of a cell is determined by its characteristic pattern of gene expression, and different cell types express overlapping but distinct sets of genes throughout development. Spatial and temporal regulation of gene expression is critical for the control of cell proliferation, cell differentiation, apoptosis, and other processes that contribute to organismal development. Furthermore, gene expression is regulated in response to extracellular signals that mediate cell-cell communication and coordinate the activities of different cell types. Appropriate gene regulation also ensures that cells function efficiently by expressing only those genes whose functions are required at a given time.

Transcriptional regulatory proteins are essential for the control of gene expression. Some of these proteins function as transcription factors that initiate, activate, repress, or terminate gene transcription. Transcription factors generally bind to promoter, enhancer, or upstream regulatory regions of a gene in a sequence-specific manner, although some factors bind regulatory elements within or downstream of the coding region. Transcription factors may bind to a specific region of DNA singly or as a complex with other accessory factors. (Reviewed in Lewin, B. (1990) Genes IV, Oxford University Press, New York, NY, pp. 554-570.)

The double helix structure and repeated sequences of DNA create topological and chemical features which can be recognized by transcription factors. These features include hydrogen bond donor and acceptor groups, hydrophobic patches, major and minor grooves, and regular repeated stretches of sequence which induce distinct bends in the helix. Typically, transcription factors recognize specific DNA sequence motifs of about 20 nucleotides in length. Multiple adjacent transcription factor-binding motifs may be required for gene regulation.

Many transcription factors incorporate DNA-binding structural motifs which comprise either α helices or ß sheets that bind to the major groove of DNA. Four well-characterized structural motifs are helix-turn-helix, zinc finger, leucine zipper, and helix-loop-helix. Proteins containing these motifs may act alone as monomers or form homo- or heterodimers that interact with DNA.

The helix-turn-helix motif consists of two α helices connected at a fixed angle by a short

chain of amino acids. One of the helices binds to the major groove. Helix-turn-helix motifs are exemplified by the homeobox motif which is present in homeodomain proteins. These proteins are critical for specifying the anterior-posterior body axis during development and are conserved throughout the animal kingdom. The Antennapedia and Ultrabithorax proteins of Drosophila melanogaster are prototypical homeodomain proteins. (Pabo, C.O. and R.T. Sauer (1992) Ann. Rev. Biochem. 61:1053-1095.)

The zinc finger motif, which binds zinc ions, generally contains tandem repeats of about 30 amino acids consisting of periodically spaced cysteine and histidine residues. Examples of this sequence pattern include the C2H2-type and the C3HC4-type zinc fingers, and the PHD domain. (Lewin, supra ; Aasland, R., et al. (1995) Trends Biochem. Sci 20:56 - 59.) Zinc finger proteins each contain an α helix and an antiparallel ß sheet whose proximity and conformation are maintained by the zinc ion. Contact with DNA is made by the arginine preceding the α helix and by the second, third, and sixth residues of the α helix. Variants of the zinc finger motif include poorly defined cysteine-rich motifs which bind zinc or other metal ions. These motifs may not contain histidine residues and are generally nonrepetitive.

The leucine zipper motif comprises a stretch of amino acids rich in leucine which can form an amphipathic α helix. This structure provides the basis for dimerization of two leucine zipper proteins. The region adjacent to the leucine zipper is usually basic, and upon protein dimerization, is optimally positioned for binding to the major groove. Proteins containing such motifs are generally referred to as bZIP transcription factors.

The helix-loop-helix motif (HLH) consists of a short α helix connected by a loop to a longer α helix. The loop is flexible and allows the two helices to fold back against each other and to bind to DNA. The transcription factor Myc contains a prototypical HLH motif.

Most transcription factors contain characteristic DNA binding motifs, and variations on the above motifs and new motifs have been and are currently being characterized. (Faisst, S. and S. Meyer (1992) Nucl. Acids Res. 20:3-26.)

Mutations in transcription factors contribute to oncogenesis. This is likely due to the role of transcription factors in the expression of genes involved in cell proliferation. For example, mutations in transcription factors encoded by proto-oncogenes, such as Fos, Jun, Myc, Rel, and Spi1, may be oncogenic due to increased stimulation of cell proliferation. Conversely, mutations in transcription factors encoded by tumor suppressor genes, such as p53, RB1, and WT1, may be oncogenic due to decreased inhibition of cell proliferation. (Latchman, D. (1995) Gene Regulation: A Eukaryotic Perspective, Chapman and Hall, London, UK, pp 242-255.)

Gene expression is also affected by chromatin-associated proteins. In the nucleus, DNA is

packaged into chromatin, the compact organization of which limits the accessibility of DNA to transcription factors and plays a key role in gene regulation. (Lewin, supra, pp. 409-410.) The compact structure of chromatin is determined and influenced by chromatin-associated proteins such as histones, high mobility group (HMG) proteins, helicases, and chromodomain proteins. There are five classes of histones, H1, H2A, H2B, H3, and H4, all of which are highly basic, low molecular weight proteins. The fundamental unit of chromatin, the nucleosome, consists of 200 base pairs of DNA associated with two copies each of H2A, H2B, H3, and H4. H1 links adjacent nucleosomes. HMG proteins are low molecular weight, non-histone proteins that may play a role in unwinding DNA and stabilizing single-stranded DNA. Helicases, which are DNA-dependent ATPases, unwind DNA, allowing access for transcription factors. Chromodomain proteins play a key role in the formation of highly-compacted, transcriptionally silent heterochromatin.

Much of the regulation of gene expression in eucaryotic cells occurs at the posttranscriptional level. Messenger RNAs (mRNA), which are produced in the cell nucleus from primary transcripts of protein-encoding genes, are processed and transported to the cytoplasm where the protein synthesis machinery is located. RNA-binding proteins are a group of proteins that participate in the processing, editing, transport, localization, and posttranscriptional regulation of mRNAs, and comprise the protein component of ribosomes as well. The RNA-binding activity of many of these proteins is mediated by a series of RNA-binding motifs identified within them. These domains include the RNP motif, the arginine-rich motif, the RGG box, and the KH motif. (Reviewed in Burd, C. G. and Dreyfuss, G. (1994) Science 265:615 - 621.) The RNP motif is the most widely found and best characterized of these motifs. The RNP motif is composed of 90-100 amino acids which form an RNA-binding domain and is found in one or more copies in proteins that bind pre-mRNA, mRNA, pre-ribosomal RNA, and small nuclear RNAs. The RNP motif is composed of two short sequences (RNP-1 and RNP-2) and a number of other mostly hydrophobic, conserved amino acids interspersed throughout the motif. (Burd, supra; ExPASy PROSITE document PDOC0030.)

Many neoplastic disorders in humans can be attributed to inappropriate gene expression. Malignant cell growth may result from either excessive expression of tumor promoting genes or insufficient expression of tumor suppressor genes. (Cleary, M.L. (1992) Cancer Surv. 15:89-104.) Chromosomal translocations may also produce chimeric loci which fuse the coding sequence of one gene with the regulatory regions of a second unrelated gene. Such an arrangement often results in inappropriate gene transcription. The Wilms tumor suppressor gene product, WT1, is a protein containing a DNA-binding domain consisting of four zinc fingers and a proline-glutamine rich region capable of regulating transcription. (ExPASy PROSITE document PR00049.) Deletions of the WT1 gene, or point mutations which destroy the DNA-binding activity of the protein are associated with development of the pediatric nephroblastoma, Wilms tumor, and Denys-Drash syndrome. (Rauscher,

F.J. (1993) FASEB J. 7:896-903.)

Certain proteins enriched in glutamine are associated with various neurological disorders including spinocerebellar ataxia, bipolar effective disorder, schizophrenia, and autism. (Margolis, R.L. et al. (1997) Human Genetics 100:114-122.) These proteins contain regions with as many as 15 or more consecutive glutamine residues and may function as transcription factors with a potential role in regulation of neurodevelopment or neuroplasticity.

The immune system responds to infection or trauma by activating a cascade of events that coordinate the progressive selection, amplification, and mobilization of cellular defense mechanisms. A complex and balanced program of gene activation and repression is involved in this process. However, hyperactivity of the immune system as a result of improper or insufficient regulation of gene expression may result in considerable tissue or organ damage. This damage is well documented in immunological responses associated with arthritis, allergens, heart attack, stroke, and infections. (Harrison's Principles of Internal Medicine, 13/e, McGraw Hill, Inc. and Teton Data Systems Software, 1996.) In particular, a zinc finger protein termed Staf50 (for Stimulated trans-acting factor of 50 kDa) is a transcriptional regulator and is induced in various cell lines by interferon-I and -II. Staf50 appears to mediate the antiviral activity of interferon by down-regulating the viral transcription directed by the long terminal repeat promoter region of human immunodeficiency virus type-1 in transfected cells. (Tissot, C. (1995) J. Biol. Chem. 270:14891-14898.)

Furthermore, the generation of multicellular organisms is based upon the induction and coordination of cell differentiation at the appropriate stages of development. Central to this process is differential gene expression, which confers the distinct identities of cells and tissues throughout the body. Failure to regulate gene expression during development could result in developmental disorders.

The discovery of new nucleic-acid binding proteins and the polynucleotides encoding them satisfies a need in the art by providing new compositions which are useful in the diagnosis, prevention, and treatment of reproductive, immune, and neurological disorders, and cell proliferative disorders including cancer.

SUMMARY OF THE INVENTION

The invention features purified polypeptides, protnames, referred to collectively as "ABBR" and individually as "NuABP-1," "NuABP-2," "NuABP-3," "NuABP-4," "NuABP-5," "NuABP-6," "NuABP-7," "NuABP-8," "NuABP-9," "NuABP-10" "NuABP-11," "NuABP-12," "NuABP-13," "NuABP-14," "NuABP-15," "NuABP-16," "NuABP-17," "NuABP-18," "NuABP-19," "NuABP-20," "NuABP-21," "NuABP-22," "NuABP-23," "NuABP-24," "NuABP-25," "NuABP-26," "NuABP-27," "NuABP-28," "NuABP-29," "NuABP-30," "NuABP-31," "NuABP-32," "NuABP-33,"

"NuABP-34," "NuABP-35," "NuABP-36," "NuABP-37," "NuABP-38," "NuABP-39," "NuABP-40" "NuABP-41," "NuABP-42," "NuABP-43," "NuABP-44," "NuABP-45," "NuABP-46," "NuABP-47," "NuABP-48," "NuABP-49," "NuABP-50" "NuABP-51," "NuABP-52," "NuABP-53," "NuABP-54," and "NuABP-55." In one aspect, the invention provides an isolated polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. In one alternative, the invention provides an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:1-55.

The invention further provides an isolated polynucleotide encoding a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. In one alternative, the polynucleotide is selected from the group consisting of SEQ ID NO:56-110.

Additionally, the invention provides a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. In one alternative, the invention provides a cell transformed with the recombinant polynucleotide. In another alternative, the invention provides a transgenic organism comprising the recombinant polynucleotide.

The invention also provides a method for producing a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. The method comprises a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said cell is transformed with a recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide encoding the polypeptide, and b) recovering the polypeptide so expressed.

Additionally, the invention provides an isolated antibody which specifically binds to a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55.

The invention further provides an isolated polynucleotide comprising a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:56-110, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:56-110, c) a polynucleotide sequence complementary to a), or d) a polynucleotide sequence complementary to b). In one alternative, the polynucleotide comprises at least 60 contiguous nucleotides.

Additionally, the invention provides a method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide comprising a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:56-110, b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:56-110, c) a polynucleotide sequence complementary to a), or d) a polynucleotide sequence complementary to b). The method comprises a) hybridizing the sample with a probe comprising at least 16 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide, and b) detecting the presence or absence of said hybridization complex, and optionally, if present, the amount thereof. In one alternative, the probe comprises at least 30 contiguous nucleotides. In another alternative, the probe comprises at least 60 contiguous nucleotides.

The invention further provides a pharmaceutical composition comprising an effective amount of a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, and a pharmaceutically acceptable excipient. The invention additionally provides a method of treating a disease or condition associated with decreased expression of functional NuABP, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention also provides a method for screening a compound for effectiveness as an agonist of a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting agonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an agonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with decreased expression of functional NuABP, comprising administering to a patient in need of such treatment the pharmaceutical composition.

Additionally, the invention provides a method for screening a compound for effectiveness as an antagonist of a polypeptide comprising a) an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55, or d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1-55. The method comprises a) exposing a sample comprising the polypeptide to a compound, and b) detecting antagonist activity in the sample. In one alternative, the invention provides a pharmaceutical composition comprising an antagonist compound identified by the method and a pharmaceutically acceptable excipient. In another alternative, the invention provides a method of treating a disease or condition associated with overexpression of functional NuABP, comprising administering to a patient in need of such treatment the pharmaceutical composition.

The invention further provides a method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence selected from the group consisting of SEQ ID NO:56-110, the method comprising a) exposing a sample comprising the target polynucleotide to a compound, and b) detecting altered expression of the target polynucleotide.

BRIEF DESCRIPTION OF THE TABLES

Table 1 shows polypeptide and nucleotide sequence identification numbers (SEQ ID NOs), clone identification numbers (clone IDs), cDNA libraries, and cDNA fragments used to assemble full-length sequences encoding NuABP.

Table 2 shows features of each polypeptide sequence, including potential motifs, homologous sequences, and methods, algorithms, and searchable databases used for analysis of NuABP.

Table 3 shows selected fragments of each nucleic acid sequence; the tissue-specific expression patterns of each nucleic acid sequence as determined by northern analysis; diseases, disorders, or conditions associated with these tissues; and the vector into which each cDNA was cloned.

Table 4 describes the tissues used to construct the cDNA libraries from which cDNA clones encoding NuABP were isolated.

Table 5 shows the tools, programs, and algorithms used to analyze NuABP, along with applicable descriptions, references, and threshold parameters.

DESCRIPTION OF THE INVENTION

Before the present proteins, nucleotide sequences, and methods are described, it is understood that this invention is not limited to the particular machines, materials and methods described, as these may vary. It is also to be understood that the terminology used herein is for the purpose of describing particular embodiments only, and is not intended to limit the scope of the present invention which will be limited only by the appended claims.

It must be noted that as used herein and in the appended claims, the singular forms "a," "an," and "the" include plural reference unless the context clearly dictates otherwise. Thus, for example, a reference to "a host cell" includes a plurality of such host cells, and a reference to "an antibody" is a reference to one or more antibodies and equivalents thereof known to those skilled in the art, and so forth.

Unless defined otherwise, all technical and scientific terms used herein have the same meanings as commonly understood by one of ordinary skill in the art to which this invention belongs. Although any machines, materials, and methods similar or equivalent to those described herein can be used to practice or test the present invention, the preferred machines, materials and methods are now described. All publications mentioned herein are cited for the purpose of describing and disclosing the cell lines, protocols, reagents and vectors which are reported in the publications and which might be used in connection with the invention. Nothing herein is to be construed as an admission that the invention is not entitled to antedate such disclosure by virtue of prior invention.

DEFINITIONS

"NuABP" refers to the amino acid sequences of substantially purified NuABP obtained from any species, particularly a mammalian species, including bovine, ovine, porcine, murine, equine, and human, and from any source, whether natural, synthetic, semi-synthetic, or recombinant.

The term "agonist" refers to a molecule which intensifies or mimics the biological activity of

NuABP. Agonists may include proteins, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of NuABP either by directly interacting with NuABP or by acting on components of the biological pathway in which NuABP participates.

An "allelic variant" is an alternative form of the gene encoding NuABP. Allelic variants may result from at least one mutation in the nucleic acid sequence and may result in altered mRNAs or in polypeptides whose structure or function may or may not be altered. A gene may have none, one, or many allelic variants of its naturally occurring form. Common mutational changes which give rise to allelic variants are generally ascribed to natural deletions, additions, or substitutions of nucleotides. Each of these types of changes may occur alone, or in combination with the others, one or more times in a given sequence.

"Altered" nucleic acid sequences encoding NuABP include those sequences with deletions, insertions, or substitutions of different nucleotides, resulting in a polypeptide the same as NuABP or a polypeptide with at least one functional characteristic of NuABP. Included within this definition are polymorphisms which may or may not be readily detectable using a particular oligonucleotide probe of the polynucleotide encoding NuABP, and improper or unexpected hybridization to allelic variants, with a locus other than the normal chromosomal locus for the polynucleotide sequence encoding NuABP. The encoded protein may also be "altered," and may contain deletions, insertions, or substitutions of amino acid residues which produce a silent change and result in a functionally equivalent NuABP. Deliberate amino acid substitutions may be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity, and/or the amphipathic nature of the residues, as long as the biological or immunological activity of NuABP is retained. For example, negatively charged amino acids may include aspartic acid and glutamic acid, and positively charged amino acids may include lysine and arginine. Amino acids with uncharged polar side chains having similar hydrophilicity values may include: asparagine and glutamine; and serine and threonine. Amino acids with uncharged side chains having similar hydrophilicity values may include: leucine, isoleucine, and valine; glycine and alanine; and phenylalanine and tyrosine.

The terms "amino acid" and "amino acid sequence" refer to an oligopeptide, peptide, polypeptide, or protein sequence, or a fragment of any of these, and to naturally occurring or synthetic molecules. Where "amino acid sequence" is recited to refer to an amino acid sequence of a naturally occurring protein molecule, "amino acid sequence" and like terms are not meant to limit the amino acid sequence to the complete native amino acid sequence associated with the recited protein molecule.

"Amplification" relates to the production of additional copies of a nucleic acid sequence. Amplification is generally carried out using polymerase chain reaction (PCR) technologies well known in the art.

The term "antagonist" refers to a molecule which inhibits or attenuates the biological activity of NuABP. Antagonists may include proteins such as antibodies, nucleic acids, carbohydrates, small molecules, or any other compound or composition which modulates the activity of NuABP either by directly interacting with NuABP or by acting on components of the biological pathway in which NuABP participates.

The term "antibody" refers to intact immunoglobulin molecules as well as to fragments thereof, such as Fab, $F(ab')_2$, and Fv fragments, which are capable of binding an epitopic determinant. Antibodies that bind NuABP polypeptides can be prepared using intact polypeptides or using fragments containing small peptides of interest as the immunizing antigen. The polypeptide or oligopeptide used to immunize an animal (e.g., a mouse, a rat, or a rabbit) can be derived from the translation of RNA, or synthesized chemically, and can be conjugated to a carrier protein if desired. Commonly used carriers that are chemically coupled to peptides include bovine serum albumin, thyroglobulin, and keyhole limpet hemocyanin (KLH). The coupled peptide is then used to immunize the animal.

The term "antigenic determinant" refers to that region of a molecule (i.e., an epitope) that makes contact with a particular antibody. When a protein or a fragment of a protein is used to immunize a host animal, numerous regions of the protein may induce the production of antibodies which bind specifically to antigenic determinants (particular regions or three-dimensional structures on the protein). An antigenic determinant may compete with the intact antigen (i.e., the immunogen used to elicit the immune response) for binding to an antibody.

The term "antisense" refers to any composition containing a nucleic acid sequence which is complementary to the "sense" strand of a specific nucleic acid sequence. Antisense molecules may be produced by any method including synthesis or transcription. Once introduced into a cell, the complementary nucleotides combine with natural sequences produced by the cell to form duplexes and to block either transcription or translation. The designation "negative" or "minus" can refer to the antisense strand, and the designation "positive" or "plus" can refer to the sense strand.

The term "biologically active" refers to a protein having structural, regulatory, or biochemical functions of a naturally occurring molecule. Likewise, "immunologically active" refers to the capability of the natural, recombinant, or synthetic NuABP, or of any oligopeptide thereof, to induce a specific immune response in appropriate animals or cells and to bind with specific antibodies.

The terms "complementary" and "complementarity" refer to the natural binding of polynucleotides by base pairing. For example, the sequence "5' A-G-T 3'" bonds to the complementary sequence "3' T-C-A 5'." Complementarity between two single-stranded molecules may be "partial," such that only some of the nucleic acids bind, or it may be "complete," such that total complementarity exists between the single stranded molecules. The degree of complementarity

between nucleic acid strands has significant effects on the efficiency and strength of the hybridization between the nucleic acid strands. This is of particular importance in amplification reactions, which depend upon binding between nucleic acid strands, and in the design and use of peptide nucleic acid (PNA) molecules.

A "composition comprising a given polynucleotide sequence" and a "composition comprising a given amino acid sequence" refer broadly to any composition containing the given polynucleotide or amino acid sequence. The composition may comprise a dry formulation or an aqueous solution. Compositions comprising polynucleotide sequences encoding NuABP or fragments of NuABP may be employed as hybridization probes. The probes may be stored in freeze-dried form and may be associated with a stabilizing agent such as a carbohydrate. In hybridizations, the probe may be deployed in an aqueous solution containing salts (e.g., NaCl), detergents (e.g., sodium dodecyl sulfate; SDS), and other components (e.g., Denhardt's solution, dry milk, salmon sperm DNA, etc.).

"Consensus sequence" refers to a nucleic acid sequence which has been resequenced to resolve uncalled bases, extended using the XL-PCR kit (Perkin-Elmer, Norwalk CT) in the 5' and/or the 3' direction, and resequenced, or which has been assembled from the overlapping sequences of one or more Incyte Clones and, in some cases, one or more public domain ESTs, using a computer program for fragment assembly, such as the GELVIEW fragment assembly system (GCG, Madison WI). Some sequences have been both extended and assembled to produce the consensus sequence.

"Conservative amino acid substitutions" are those substitutions that, when made, least interfere with the properties of the original protein, i.e., the structure and especially the function of the protein is conserved and not significantly changed by such substitutions. The table below shows amino acids which may be substituted for an original amino acid in a protein and which are regarded as conservative amino acid substitutions.

Original Residue	Conservative Substitution
Ala	Gly, Ser
Arg	His, Lys
Asn	Asp, Gln, His
Asp	Asn, Glu
Cys	Ala, Ser
Gln	Asn, Glu, His
Glu	Asp, Gln, His
Gly	Ala
His	Asn, Arg, Gln, Glu
Ile	Leu, Val
Leu	Ile, Val
Lys	Arg, Gln, Glu
Met	Leu, Ile
Phe	His, Met, Leu, Trp, Tyr
Ser	Cys, Thr
Thr	Ser, Val

Trp	Phe, Tyr
Tyr	His, Phe, Trp
Val	Ile, Leu, Thr

Conservative amino acid substitutions generally maintain (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a beta sheet or alpha helical conformation, (b) the charge or hydrophobicity of the molecule at the site of the substitution, and/or (c) the bulk of the side chain.

A "deletion" refers to a change in the amino acid or nucleotide sequence that results in the absence of one or more amino acid residues or nucleotides.

The term "derivative" refers to the chemical modification of a polypeptide sequence, or a polynucleotide sequence. Chemical modifications of a polynucleotide sequence can include, for example, replacement of hydrogen by an alkyl, acyl, hydroxyl, or amino group. A derivative polynucleotide encodes a polypeptide which retains at least one biological or immunological function of the natural molecule. A derivative polypeptide is one modified by glycosylation, pegylation, or any similar process that retains at least one biological or immunological function of the polypeptide from which it was derived.

A "fragment" is a unique portion of NuABP or the polynucleotide encoding NuABP which is identical in sequence to but shorter in length than the parent sequence. A fragment may comprise up to the entire length of the defined sequence, minus one nucleotide/amino acid residue. For example, a fragment may comprise from 5 to 1000 contiguous nucleotides or amino acid residues. A fragment used as a probe, primer, antigen, therapeutic molecule, or for other purposes, may be at least 5, 10, 15, 20, 25, 30, 40, 50, 60, 75, 100, 150, 250 or at least 500 contiguous nucleotides or amino acid residues in length. Fragments may be preferentially selected from certain regions of a molecule. For example, a polypeptide fragment may comprise a certain length of contiguous amino acids selected from the first 250 or 500 amino acids (or first 25% or 50% of a polypeptide) as shown in a certain defined sequence. Clearly these lengths are exemplary, and any length that is supported by the specification, including the Sequence Listing, tables, and figures, may be encompassed by the present embodiments.

A fragment of SEQ ID NO:56-110 comprises a region of unique polynucleotide sequence that specifically identifies SEQ ID NO:56-110, for example, as distinct from any other sequence in the same genome. A fragment of SEQ ID NO:56-110 is useful, for example, in hybridization and amplification technologies and in analogous methods that distinguish SEQ ID NO:56-110 from related polynucleotide sequences. The precise length of a fragment of SEQ ID NO:56-110 and the region of SEQ ID NO:56-110 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

A fragment of SEQ ID NO:1-55 is encoded by a fragment of SEQ ID NO:56-110. A

fragment of SEQ ID NO:1-55 comprises a region of unique amino acid sequence that specifically identifies SEQ ID NO:1-55. For example, a fragment of SEQ ID NO:1-55 is useful as an immunogenic peptide for the development of antibodies that specifically recognize SEQ ID NO:1-55. The precise length of a fragment of SEQ ID NO:1-55 and the region of SEQ ID NO:1-55 to which the fragment corresponds are routinely determinable by one of ordinary skill in the art based on the intended purpose for the fragment.

The term "similarity" refers to a degree of complementarity. There may be partial similarity or complete similarity. The word "identity" may substitute for the word "similarity." A partially complementary sequence that at least partially inhibits an identical sequence from hybridizing to a target nucleic acid is referred to as "substantially similar." The inhibition of hybridization of the completely complementary sequence to the target sequence may be examined using a hybridization assay (Southern or northern blot, solution hybridization, and the like) under conditions of reduced stringency. A substantially similar sequence or hybridization probe will compete for and inhibit the binding of a completely similar (identical) sequence to the target sequence under conditions of reduced stringency. This is not to say that conditions of reduced stringency are such that non-specific binding is permitted, as reduced stringency conditions require that the binding of two sequences to one another be a specific (i.e., a selective) interaction. The absence of non-specific binding may be tested by the use of a second target sequence which lacks even a partial degree of complementarity (e.g., less than about 30% similarity or identity). In the absence of non-specific binding, the substantially similar sequence or probe will not hybridize to the second non-complementary target sequence.

The phrases "percent identity" and "% identity," as applied to polynucleotide sequences, refer to the percentage of residue matches between at least two polynucleotide sequences aligned using a standardized algorithm. Such an algorithm may insert, in a standardized and reproducible way, gaps in the sequences being compared in order to optimize alignment between two sequences, and therefore achieve a more meaningful comparison of the two sequences.

Percent identity between polynucleotide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program. This program is part of the LASERGENE software package, a suite of molecular biological analysis programs (DNASTAR, Madison WI). CLUSTAL V is described in Higgins, D.G. and P.M. Sharp (1989) CABIOS 5:151-153 and in Higgins, D.G. et al. (1992) CABIOS 8:189-191. For pairwise alignments of polynucleotide sequences, the default parameters are set as follows: Ktuple=2, gap penalty=5, window=4, and "diagonals saved"=4. The "weighted" residue weight table is selected as the default. Percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polynucleotide sequence pairs.

Alternatively, a suite of commonly used and freely available sequence comparison algorithms is provided by the National Center for Biotechnology Information (NCBI) Basic Local Alignment Search Tool (BLAST) (Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410), which is available from several sources, including the NCBI, Bethesda, MD, and on the Internet at http://www.ncbi.nlm.nih.gov/BLAST/. The BLAST software suite includes various sequence analysis programs including "blastn," that is used to align a known polynucleotide sequence with other polynucleotide sequences from a variety of databases. Also available is a tool called "BLAST 2 Sequences" that is used for direct pairwise comparison of two nucleotide sequences. "BLAST 2 Sequences" can be accessed and used interactively at http://www.ncbi.nlm.nih.gov/gorf/bl2.html. The "BLAST 2 Sequences" tool can be used for both blastn and blastp (discussed below). BLAST programs are commonly used with gap and other parameters set to default settings. For example, to compare two nucleotide sequences, one may use blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62
Reward for match: 1
Penalty for mismatch: -2
Open Gap: 5 and Extension Gap: 2 penalties
Gap x drop-off: 50
Expect: 10
Word Size: 11
Filter: on

Percent identity may be measured over the length of an entire defined sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined sequence, for instance, a fragment of at least 20, at least 30, at least 40, at least 50, at least 70, at least 100, or at least 200 contiguous nucleotides. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures, or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

Nucleic acid sequences that do not show a high degree of identity may nevertheless encode similar amino acid sequences due to the degeneracy of the genetic code. It is understood that changes in a nucleic acid sequence can be made using this degeneracy to produce multiple nucleic acid sequences that all encode substantially the same protein.

The phrases "percent identity" and "% identity," as applied to polypeptide sequences, refer to the percentage of residue matches between at least two polypeptide sequences aligned using a standardized algorithm. Methods of polypeptide sequence alignment are well-known. Some

alignment methods take into account conservative amino acid substitutions. Such conservative substitutions, explained in more detail above, generally preserve the hydrophobicity and acidity at the site of substitution, thus preserving the structure (and therefore function) of the polypeptide.

Percent identity between polypeptide sequences may be determined using the default parameters of the CLUSTAL V algorithm as incorporated into the MEGALIGN version 3.12e sequence alignment program (described and referenced above). For pairwise alignments of polypeptide sequences using CLUSTAL V, the default parameters are set as follows: Ktuple=1, gap penalty=3, window=5, and "diagonals saved"=5. The PAM250 matrix is selected as the default residue weight table. As with polynucleotide alignments, the percent identity is reported by CLUSTAL V as the "percent similarity" between aligned polypeptide sequence pairs.

Alternatively the NCBI BLAST software suite may be used. For example, for a pairwise comparison of two polypeptide sequences, one may use the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) with blastp set at default parameters. Such default parameters may be, for example:

Matrix: BLOSUM62

Open Gap: 11 and Extension Gap: 1 penalties

Gap x drop-off: 50

Expect: 10

Word Size: 3

Filter: on

Percent identity may be measured over the length of an entire defined polypeptide sequence, for example, as defined by a particular SEQ ID number, or may be measured over a shorter length, for example, over the length of a fragment taken from a larger, defined polypeptide sequence, for instance, a fragment of at least 15, at least 20, at least 30, at least 40, at least 50, at least 70 or at least 150 contiguous residues. Such lengths are exemplary only, and it is understood that any fragment length supported by the sequences shown herein, in the tables, figures or Sequence Listing, may be used to describe a length over which percentage identity may be measured.

"Human artificial chromosomes" (HACs) are linear microchromosomes which may contain DNA sequences of about 6 kb to 10 Mb in size, and which contain all of the elements required for stable mitotic chromosome segregation and maintenance.

The term "humanized antibody" refers to antibody molecules in which the amino acid sequence in the non-antigen binding regions has been altered so that the antibody more closely resembles a human antibody, and still retains its original binding ability.

"Hybridization" refers to the process by which a polynucleotide strand anneals with a complementary strand through base pairing under defined hybridization conditions. Specific hybridization is an indication that two nucleic acid sequences share a high degree of identity. Specific

hybridization complexes form under permissive annealing conditions and remain hybridized after the "washing" step(s). The washing step(s) is particularly important in determining the stringency of the hybridization process, with more stringent conditions allowing less non-specific binding, i.e., binding between pairs of nucleic acid strands that are not perfectly matched. Permissive conditions for annealing of nucleic acid sequences are routinely determinable by one of ordinary skill in the art and may be consistent among hybridization experiments, whereas wash conditions may be varied among experiments to achieve the desired stringency, and therefore hybridization specificity. Permissive annealing conditions occur, for example, at 68°C in the presence of about 6 x SSC, about 1% (w/v) SDS, and about 100 µg/ml denatured salmon sperm DNA.

Generally, stringency of hybridization is expressed, in part, with reference to the temperature under which the wash step is carried out. Generally, such wash temperatures are selected to be about 5°C to 20°C lower than the thermal melting point (T_m) for the specific sequence at a defined ionic strength and pH. The T_m is the temperature (under defined ionic strength and pH) at which 50% of the target sequence hybridizes to a perfectly matched probe. An equation for calculating T_m and conditions for nucleic acid hybridization are well known and can be found in Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; specifically see volume 2, chapter 9.

High stringency conditions for hybridization between polynucleotides of the present invention include wash conditions of 68°C in the presence of about 0.2 x SSC and about 0.1% SDS, for 1 hour. Alternatively, temperatures of about 65°C, 60°C, 55°C, or 42°C may be used. SSC concentration may be varied from about 0.1 to 2 x SSC, with SDS being present at about 0.1%. Typically, blocking reagents are used to block non-specific hybridization. Such blocking reagents include, for instance, denatured salmon sperm DNA at about 100-200 µg/ml. Organic solvent, such as formamide at a concentration of about 35-50% v/v, may also be used under particular circumstances, such as for RNA:DNA hybridizations. Useful variations on these wash conditions will be readily apparent to those of ordinary skill in the art. Hybridization, particularly under high stringency conditions, may be suggestive of evolutionary similarity between the nucleotides. Such similarity is strongly indicative of a similar role for the nucleotides and their encoded polypeptides.

The term "hybridization complex" refers to a complex formed between two nucleic acid sequences by virtue of the formation of hydrogen bonds between complementary bases. A hybridization complex may be formed in solution (e.g., C_0t or R_0t analysis) or formed between one nucleic acid sequence present in solution and another nucleic acid sequence immobilized on a solid support (e.g., paper, membranes, filters, chips, pins or glass slides, or any other appropriate substrate to which cells or their nucleic acids have been fixed).

The words "insertion" and "addition" refer to changes in an amino acid or nucleotide

sequence resulting in the addition of one or more amino acid residues or nucleotides, respectively.

"Immune response" can refer to conditions associated with inflammation, trauma, immune disorders, or infectious or genetic disease, etc. These conditions can be characterized by expression of various factors, e.g., cytokines, chemokines, and other signaling molecules, which may affect cellular and systemic defense systems.

The term "microarray" refers to an arrangement of distinct polynucleotides on a substrate.

The terms "element" and "array element" in a microarray context, refer to hybridizable polynucleotides arranged on the surface of a substrate.

The term "modulate" refers to a change in the activity of NuABP. For example, modulation may cause an increase or a decrease in protein activity, binding characteristics, or any other biological, functional, or immunological properties of NuABP.

The phrases "nucleic acid" and "nucleic acid sequence" refer to a nucleotide, oligonucleotide, polynucleotide, or any fragment thereof. These phrases also refer to DNA or RNA of genomic or synthetic origin which may be single-stranded or double-stranded and may represent the sense or the antisense strand, to peptide nucleic acid (PNA), or to any DNA-like or RNA-like material.

"Operably linked" refers to the situation in which a first nucleic acid sequence is placed in a functional relationship with the second nucleic acid sequence. For instance, a promoter is operably linked to a coding sequence if the promoter affects the transcription or expression of the coding sequence. Generally, operably linked DNA sequences may be in close proximity or contiguous and, where necessary to join two protein coding regions, in the same reading frame.

"Peptide nucleic acid" (PNA) refers to an antisense molecule or anti-gene agent which comprises an oligonucleotide of at least about 5 nucleotides in length linked to a peptide backbone of amino acid residues ending in lysine. The terminal lysine confers solubility to the composition. PNAs preferentially bind complementary single stranded DNA or RNA and stop transcript elongation, and may be pegylated to extend their lifespan in the cell.

"Probe" refers to nucleic acid sequences encoding NuABP, their complements, or fragments thereof, which are used to detect identical, allelic or related nucleic acid sequences. Probes are isolated oligonucleotides or polynucleotides attached to a detectable label or reporter molecule. Typical labels include radioactive isotopes, ligands, chemiluminescent agents, and enzymes. "Primers" are short nucleic acids, usually DNA oligonucleotides, which may be annealed to a target polynucleotide by complementary base-pairing. The primer may then be extended along the target DNA strand by a DNA polymerase enzyme. Primer pairs can be used for amplification (and identification) of a nucleic acid sequence, e.g., by the polymerase chain reaction (PCR).

Probes and primers as used in the present invention typically comprise at least 15 contiguous nucleotides of a known sequence. In order to enhance specificity, longer probes and primers may also

be employed, such as probes and primers that comprise at least 20, 25, 30, 40, 50, 60, 70, 80, 90, 100, or at least 150 consecutive nucleotides of the disclosed nucleic acid sequences. Probes and primers may be considerably longer than these examples, and it is understood that any length supported by the specification, including the tables, figures, and Sequence Listing, may be used.

Methods for preparing and using probes and primers are described in the references, for example Sambrook et al., 1989, Molecular Cloning: A Laboratory Manual, 2nd ed., vol. 1-3, Cold Spring Harbor Press, Plainview NY; Ausubel et al.,1987, Current Protocols in Molecular Biology, Greene Publ. Assoc. & Wiley-Intersciences, New York NY; Innis et al., 1990, PCR Protocols, A Guide to Methods and Applications, Academic Press, San Diego CA. PCR primer pairs can be derived from a known sequence, for example, by using computer programs intended for that purpose such as Primer (Version 0.5, 1991, Whitehead Institute for Biomedical Research, Cambridge MA).

Oligonucleotides for use as primers are selected using software known in the art for such purpose. For example, OLIGO 4.06 software is useful for the selection of PCR primer pairs of up to 100 nucleotides each, and for the analysis of oligonucleotides and larger polynucleotides of up to 5,000 nucleotides from an input polynucleotide sequence of up to 32 kilobases. Similar primer selection programs have incorporated additional features for expanded capabilities. For example, the PrimOU primer selection program (available to the public from the Genome Center at University of Texas South West Medical Center, Dallas TX) is capable of choosing specific primers from megabase sequences and is thus useful for designing primers on a genome-wide scope. The Primer3 primer selection program (available to the public from the Whitehead Institute/MIT Center for Genome Research, Cambridge MA) allows the user to input a "mispriming library," in which sequences to avoid as primer binding sites are user-specified. Primer3 is useful, in particular, for the selection of oligonucleotides for microarrays. (The source code for the latter two primer selection programs may also be obtained from their respective sources and modified to meet the user's specific needs.) The PrimeGen program (available to the public from the UK Human Genome Mapping Project Resource Centre, Cambridge UK) designs primers based on multiple sequence alignments, thereby allowing selection of primers that hybridize to either the most conserved or least conserved regions of aligned nucleic acid sequences. Hence, this program is useful for identification of both unique and conserved oligonucleotides and polynucleotide fragments. The oligonucleotides and polynucleotide fragments identified by any of the above selection methods are useful in hybridization technologies, for example, as PCR or sequencing primers, microarray elements, or specific probes to identify fully or partially complementary polynucleotides in a sample of nucleic acids. Methods of oligonucleotide selection are not limited to those described above.

A "recombinant nucleic acid" is a sequence that is not naturally occurring or has a sequence that is made by an artificial combination of two or more otherwise separated segments of sequence.

This artificial combination is often accomplished by chemical synthesis or, more commonly, by the artificial manipulation of isolated segments of nucleic acids, e.g., by genetic engineering techniques such as those described in Sambrook, supra. The term recombinant includes nucleic acids that have been altered solely by addition, substitution, or deletion of a portion of the nucleic acid. Frequently, a recombinant nucleic acid may include a nucleic acid sequence operably linked to a promoter sequence. Such a recombinant nucleic acid may be part of a vector that is used, for example, to transform a cell.

Alternatively, such recombinant nucleic acids may be part of a viral vector, e.g., based on a vaccinia virus, that could be use to vaccinate a mammal wherein the recombinant nucleic acid is expressed, inducing a protective immunological response in the mammal.

The term "sample" is used in its broadest sense. A sample suspected of containing nucleic acids encoding NuABP, or fragments thereof, or NuABP itself, may comprise a bodily fluid; an extract from a cell, chromosome, organelle, or membrane isolated from a cell; a cell; genomic DNA, RNA, or cDNA, in solution or bound to a substrate; a tissue; a tissue print; etc.

The terms "specific binding" and "specifically binding" refer to that interaction between a protein or peptide and an agonist, an antibody, an antagonist, a small molecule, or any natural or synthetic binding composition. The interaction is dependent upon the presence of a particular structure of the protein, e.g., the antigenic determinant or epitope, recognized by the binding molecule. For example, if an antibody is specific for epitope "A," the presence of a polypeptide containing the epitope A, or the presence of free unlabeled A, in a reaction containing free labeled A and the antibody will reduce the amount of labeled A that binds to the antibody.

The term "substantially purified" refers to nucleic acid or amino acid sequences that are removed from their natural environment and are isolated or separated, and are at least 60% free, preferably at least 75% free, and most preferably at least 90% free from other components with which they are naturally associated.

A "substitution" refers to the replacement of one or more amino acids or nucleotides by different amino acids or nucleotides, respectively.

"Substrate" refers to any suitable rigid or semi-rigid support including membranes, filters, chips, slides, wafers, fibers, magnetic or nonmagnetic beads, gels, tubing, plates, polymers, microparticles and capillaries. The substrate can have a variety of surface forms, such as wells, trenches, pins, channels and pores, to which polynucleotides or polypeptides are bound.

"Transformation" describes a process by which exogenous DNA enters and changes a recipient cell. Transformation may occur under natural or artificial conditions according to various methods well known in the art, and may rely on any known method for the insertion of foreign nucleic acid sequences into a prokaryotic or eukaryotic host cell. The method for transformation is selected

based on the type of host cell being transformed and may include, but is not limited to, viral infection, electroporation, heat shock, lipofection, and particle bombardment. The term "transformed" cells includes stably transformed cells in which the inserted DNA is capable of replication either as an autonomously replicating plasmid or as part of the host chromosome, as well as transiently transformed cells which express the inserted DNA or RNA for limited periods of time.

A "variant" of a particular nucleic acid sequence is defined as a nucleic acid sequence having at least 40% sequence identity to the particular nucleic acid sequence over a certain length of one of the nucleic acid sequences using blastn with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of nucleic acids may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 85%, at least 90%, at least 95% or at least 98% or greater sequence identity over a certain defined length. A variant may be described as, for example, an "allelic" (as defined above), "splice," "species," or "polymorphic" variant. A splice variant may have significant identity to a reference molecule, but will generally have a greater or lesser number of polynucleotides due to alternate splicing of exons during mRNA processing. The corresponding polypeptide may possess additional functional domains or lack domains that are present in the reference molecule. Species variants are polynucleotide sequences that vary from one species to another. The resulting polypeptides generally will have significant amino acid identity relative to each other. A polymorphic variant is a variation in the polynucleotide sequence of a particular gene between individuals of a given species. Polymorphic variants also may encompass "single nucleotide polymorphisms" (SNPs) in which the polynucleotide sequence varies by one nucleotide base. The presence of SNPs may be indicative of, for example, a certain population, a disease state, or a propensity for a disease state.

A "variant" of a particular polypeptide sequence is defined as a polypeptide sequence having at least 40% sequence identity to the particular polypeptide sequence over a certain length of one of the polypeptide sequences using blastp with the "BLAST 2 Sequences" tool Version 2.0.9 (May-07-1999) set at default parameters. Such a pair of polypeptides may show, for example, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95%, or at least 98% or greater sequence identity over a certain defined length of one of the polypeptides.

THE INVENTION

The invention is based on the discovery of new human nucleic-acid binding proteins (NuABP), the polynucleotides encoding NuABP, and the use of these compositions for the diagnosis, treatment, or prevention of reproductive, immune, and neurological disorders, and cell proliferative disorders including cancer.

Table 1 lists the Incyte clones used to assemble full length nucleotide sequences encoding

NuABP. Columns 1 and 2 show the sequence identification numbers (SEQ ID NOs) of the polypeptide and nucleotide sequences, respectively. Column 3 shows the clone IDs of the Incyte clones in which nucleic acids encoding each NuABP were identified, and column 4 shows the cDNA libraries from which these clones were isolated. Column 5 shows Incyte clones and their corresponding cDNA libraries. Clones for which cDNA libraries are not indicated were derived from pooled cDNA libraries. The Incyte clones in column 5 were used to assemble the consensus nucleotide sequence of each NuABP and are useful as fragments in hybridization technologies.

The columns of Table 2 show various properties of each of the polypeptides of the invention: column 1 references the SEQ ID NO; column 2 shows the number of amino acid residues in each polypeptide; column 3 shows potential phosphorylation sites; column 4 shows potential glycosylation sites; column 5 shows the amino acid residues comprising signature sequences and motifs; column 6 shows identification or homologous sequences as identified by BLAST analysis; and column 7 shows analytical methods and in some cases, searchable databases to which the analytical methods were applied. The methods of column 7 were used to characterize each polypeptide through sequence homology and protein motifs.

The columns of Table 3 show the tissue-specificity and diseases, disorders, or conditions associated with nucleotide sequences encoding NuABP. The first column of Table 3 lists the nucleotide SEQ ID NOs. Column 2 lists fragments of the nucleotide sequences of column 1. These fragments are useful, for example, in hybridization or amplification technologies to identify SEQ ID NO:56-110 and to distinguish between SEQ ID NO:56-110 and related polynucleotide sequences. The polypeptides encoded by these fragments are useful, for example, as immunogenic peptides. Column 3 lists tissue categories which express NuABP as a fraction of total tissues expressing NuABP. Column 4 lists diseases, disorders, or conditions associated with those tissues expressing NuABP as a fraction of total tissues expressing NuABP. Of particular note is the expression of SEQ ID NO:83 and SEQ ID NO:110 in neurological tissue. About 53% of the cDNA libraries expressing SEQ ID NO:83 are derived from neurological tissue. Furthermore, SEQ ID NO:110 expression is detected exclusively in a cDNA library derived from brain tissue afflicted with Huntington's disease. Column 5 lists the vectors used to subclone each cDNA library.

The columns of Table 4 show descriptions of the tissues used to construct the cDNA libraries from which cDNA clones encoding NuABP were isolated. Column 1 references the nucleotide SEQ ID NOs, column 2 shows the cDNA libraries from which these clones were isolated, and column 3 shows the tissue origins and other descriptive information relevant to the cDNA libraries in column 2.

Fragments of the nucleotide sequences encoding NuABP are useful, for example, in hybridization or amplification technologies to identify SEQ ID NOS:56-110 and to distinguish between SEQ ID NOS:56-110 and related polynucleotide sequences. The polypeptides encoded by

these fragments are useful, for example, as immunogenic peptides.

The invention also encompasses NuABP variants. A preferred NuABP variant is one which has at least about 80%, or alternatively at least about 90%, or even at least about 95% amino acid sequence identity to the NuABP amino acid sequence, and which contains at least one functional or structural characteristic of NuABP.

The invention also encompasses polynucleotides which encode NuABP. In a particular embodiment, the invention encompasses a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:56-110, which encodes NuABP.

The invention also encompasses a variant of a polynucleotide sequence encoding NuABP. In particular, such a variant polynucleotide sequence will have at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to the polynucleotide sequence encoding NuABP. A particular aspect of the invention encompasses a variant of a polynucleotide sequence comprising a sequence selected from the group consisting of SEQ ID NO:56-110 which has at least about 70%, or alternatively at least about 85%, or even at least about 95% polynucleotide sequence identity to a nucleic acid sequence selected from the group consisting of SEQ ID NO:56-110. Any one of the polynucleotide variants described above can encode an amino acid sequence which contains at least one functional or structural characteristic of NuABP.

It will be appreciated by those skilled in the art that as a result of the degeneracy of the genetic code, a multitude of polynucleotide sequences encoding NuABP, some bearing minimal similarity to the polynucleotide sequences of any known and naturally occurring gene, may be produced. Thus, the invention contemplates each and every possible variation of polynucleotide sequence that could be made by selecting combinations based on possible codon choices. These combinations are made in accordance with the standard triplet genetic code as applied to the polynucleotide sequence of naturally occurring NuABP, and all such variations are to be considered as being specifically disclosed.

Although nucleotide sequences which encode NuABP and its variants are generally capable of hybridizing to the nucleotide sequence of the naturally occurring NuABP under appropriately selected conditions of stringency, it may be advantageous to produce nucleotide sequences encoding NuABP or its derivatives possessing a substantially different codon usage, e.g., inclusion of non-naturally occurring codons. Codons may be selected to increase the rate at which expression of the peptide occurs in a particular prokaryotic or eukaryotic host in accordance with the frequency with which particular codons are utilized by the host. Other reasons for substantially altering the nucleotide sequence encoding NuABP and its derivatives without altering the encoded amino acid sequences include the production of RNA transcripts having more desirable properties, such as a greater half-life, than transcripts produced from the naturally occurring sequence.

The invention also encompasses production of DNA sequences which encode NuABP and NuABP derivatives, or fragments thereof, entirely by synthetic chemistry. After production, the synthetic sequence may be inserted into any of the many available expression vectors and cell systems using reagents well known in the art. Moreover, synthetic chemistry may be used to introduce mutations into a sequence encoding NuABP or any fragment thereof.

Also encompassed by the invention are polynucleotide sequences that are capable of hybridizing to the claimed polynucleotide sequences, and, in particular, to those shown in SEQ ID NO:56-110 and fragments thereof under various conditions of stringency. (See, e.g., Wahl, G.M. and S.L. Berger (1987) Methods Enzymol. 152:399-407; Kimmel, A.R. (1987) Methods Enzymol. 152:507-511.) Hybridization conditions, including annealing and wash conditions, are described in "Definitions."

Methods for DNA sequencing are well known in the art and may be used to practice any of the embodiments of the invention. The methods may employ such enzymes as the Klenow fragment of DNA polymerase I, SEQUENASE (US Biochemical, Cleveland OH), Taq polymerase (Perkin-Elmer), thermostable T7 polymerase (Amersham Pharmacia Biotech, Piscataway NJ), or combinations of polymerases and proofreading exonucleases such as those found in the ELONGASE amplification system (Life Technologies, Gaithersburg MD). Preferably, sequence preparation is automated with machines such as the MICROLAB 2200 liquid transfer system (Hamilton, Reno NV), PTC200 thermal cycler (MJ Research, Watertown MA) and ABI CATALYST 800 thermal cycler (Perkin-Elmer). Sequencing is then carried out using either the ABI 373 or 377 DNA sequencing system (Perkin-Elmer), the MEGABACE 1000 DNA sequencing system (Molecular Dynamics, Sunnyvale CA), or other systems known in the art. The resulting sequences are analyzed using a variety of algorithms which are well known in the art. (See, e.g., Ausubel, F.M. (1997) Short Protocols in Molecular Biology, John Wiley & Sons, New York NY, unit 7.7; Meyers, R.A. (1995) Molecular Biology and Biotechnology, Wiley VCH, New York NY, pp. 856-853.)

The nucleic acid sequences encoding NuABP may be extended utilizing a partial nucleotide sequence and employing various PCR-based methods known in the art to detect upstream sequences, such as promoters and regulatory elements. For example, one method which may be employed, restriction-site PCR, uses universal and nested primers to amplify unknown sequence from genomic DNA within a cloning vector. (See, e.g., Sarkar, G. (1993) PCR Methods Applic. 2:318-322.) Another method, inverse PCR, uses primers that extend in divergent directions to amplify unknown sequence from a circularized template. The template is derived from restriction fragments comprising a known genomic locus and surrounding sequences. (See, e.g., Triglia, T. et al. (1988) Nucleic Acids Res. 16:8186.) A third method, capture PCR, involves PCR amplification of DNA fragments adjacent to known sequences in human and yeast artificial chromosome DNA. (See, e.g., Lagerstrom, M. et al.

(1991) PCR Methods Applic. 1:111-119.) In this method, multiple restriction enzyme digestions and ligations may be used to insert an engineered double-stranded sequence into a region of unknown sequence before performing PCR. Other methods which may be used to retrieve unknown sequences are known in the art. (See, e.g., Parker, J.D. et al. (1991) Nucleic Acids Res. 19:3055-3060). Additionally, one may use PCR, nested primers, and PROMOTERFINDER libraries (Clontech, Palo Alto CA) to walk genomic DNA. This procedure avoids the need to screen libraries and is useful in finding intron/exon junctions. For all PCR-based methods, primers may be designed using commercially available software, such as OLIGO 4.06 Primer Analysis software (National Biosciences, Plymouth MN) or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the template at temperatures of about 68°C to 72°C.

When screening for full-length cDNAs, it is preferable to use libraries that have been size-selected to include larger cDNAs. In addition, random-primed libraries, which often include sequences containing the 5' regions of genes, are preferable for situations in which an oligo d(T) library does not yield a full-length cDNA. Genomic libraries may be useful for extension of sequence into 5' non-transcribed regulatory regions.

Capillary electrophoresis systems which are commercially available may be used to analyze the size or confirm the nucleotide sequence of sequencing or PCR products. In particular, capillary sequencing may employ flowable polymers for electrophoretic separation, four different nucleotide-specific, laser-stimulated fluorescent dyes, and a charge coupled device camera for detection of the emitted wavelengths. Output/light intensity may be converted to electrical signal using appropriate software (e.g., GENOTYPER and SEQUENCE NAVIGATOR, Perkin-Elmer), and the entire process from loading of samples to computer analysis and electronic data display may be computer controlled. Capillary electrophoresis is especially preferable for sequencing small DNA fragments which may be present in limited amounts in a particular sample.

In another embodiment of the invention, polynucleotide sequences or fragments thereof which encode NuABP may be cloned in recombinant DNA molecules that direct expression of NuABP, or fragments or functional equivalents thereof, in appropriate host cells. Due to the inherent degeneracy of the genetic code, other DNA sequences which encode substantially the same or a functionally equivalent amino acid sequence may be produced and used to express NuABP.

The nucleotide sequences of the present invention can be engineered using methods generally known in the art in order to alter NuABP-encoding sequences for a variety of purposes including, but not limited to, modification of the cloning, processing, and/or expression of the gene product. DNA shuffling by random fragmentation and PCR reassembly of gene fragments and synthetic oligonucleotides may be used to engineer the nucleotide sequences. For example, oligonucleotide-

mediated site-directed mutagenesis may be used to introduce mutations that create new restriction sites, alter glycosylation patterns, change codon preference, produce splice variants, and so forth.

In another embodiment, sequences encoding NuABP may be synthesized, in whole or in part, using chemical methods well known in the art. (See, e.g., Caruthers, M.H. et al. (1980) Nucleic Acids Symp. Ser. 7:215-223; and Horn, T. et al. (1980) Nucleic Acids Symp. Ser. 7:225-232.) Alternatively, NuABP itself or a fragment thereof may be synthesized using chemical methods. For example, peptide synthesis can be performed using various solid-phase techniques. (See, e.g., Roberge, J.Y. et al. (1995) Science 269:202-204.) Automated synthesis may be achieved using the ABI 431A peptide synthesizer (Perkin-Elmer). Additionally, the amino acid sequence of NuABP, or any part thereof, may be altered during direct synthesis and/or combined with sequences from other proteins, or any part thereof, to produce a variant polypeptide.

The peptide may be substantially purified by preparative high performance liquid chromatography. (See, e.g., Chiez, R.M. and F.Z. Regnier (1990) Methods Enzymol. 182:392-421.) The composition of the synthetic peptides may be confirmed by amino acid analysis or by sequencing. (See, e.g., Creighton, T. (1984) Proteins, Structures and Molecular Properties, WH Freeman, New York NY.)

In order to express a biologically active NuABP, the nucleotide sequences encoding NuABP or derivatives thereof may be inserted into an appropriate expression vector, i.e., a vector which contains the necessary elements for transcriptional and translational control of the inserted coding sequence in a suitable host. These elements include regulatory sequences, such as enhancers, constitutive and inducible promoters, and 5' and 3' untranslated regions in the vector and in polynucleotide sequences encoding NuABP. Such elements may vary in their strength and specificity. Specific initiation signals may also be used to achieve more efficient translation of sequences encoding NuABP. Such signals include the ATG initiation codon and adjacent sequences, e.g. the Kozak sequence. In cases where sequences encoding NuABP and its initiation codon and upstream regulatory sequences are inserted into the appropriate expression vector, no additional transcriptional or translational control signals may be needed. However, in cases where only coding sequence, or a fragment thereof, is inserted, exogenous translational control signals including an in-frame ATG initiation codon should be provided by the vector. Exogenous translational elements and initiation codons may be of various origins, both natural and synthetic. The efficiency of expression may be enhanced by the inclusion of enhancers appropriate for the particular host cell system used. (See, e.g., Scharf, D. et al. (1994) Results Probl. Cell Differ. 20:125-162.)

Methods which are well known to those skilled in the art may be used to construct expression vectors containing sequences encoding NuABP and appropriate transcriptional and translational control elements. These methods include in vitro recombinant DNA techniques, synthetic techniques,

and in vivo genetic recombination. (See, e.g., Sambrook, J. et al. (1989) Molecular Cloning, A Laboratory Manual, Cold Spring Harbor Press, Plainview NY, ch. 4, 8, and 16-17; Ausubel, F.M. et al. (1995) Current Protocols in Molecular Biology, John Wiley & Sons, New York NY, ch. 9, 13, and 16.)

A variety of expression vector/host systems may be utilized to contain and express sequences encoding NuABP. These include, but are not limited to, microorganisms such as bacteria transformed with recombinant bacteriophage, plasmid, or cosmid DNA expression vectors; yeast transformed with yeast expression vectors; insect cell systems infected with viral expression vectors (e.g., baculovirus); plant cell systems transformed with viral expression vectors (e.g., cauliflower mosaic virus, CaMV, or tobacco mosaic virus, TMV) or with bacterial expression vectors (e.g., Ti or pBR322 plasmids); or animal cell systems. The invention is not limited by the host cell employed.

In bacterial systems, a number of cloning and expression vectors may be selected depending upon the use intended for polynucleotide sequences encoding NuABP. For example, routine cloning, subcloning, and propagation of polynucleotide sequences encoding NuABP can be achieved using a multifunctional E. coli vector such as PBLUESCRIPT (Stratagene, La Jolla CA) or PSPORT1 plasmid (Life Technologies). Ligation of sequences encoding NuABP into the vector's multiple cloning site disrupts the *lacZ* gene, allowing a colorimetric screening procedure for identification of transformed bacteria containing recombinant molecules. In addition, these vectors may be useful for in vitro transcription, dideoxy sequencing, single strand rescue with helper phage, and creation of nested deletions in the cloned sequence. (See, e.g., Van Heeke, G. and S.M. Schuster (1989) J. Biol. Chem. 264:5503-5509.) When large quantities of NuABP are needed, e.g. for the production of antibodies, vectors which direct high level expression of NuABP may be used. For example, vectors containing the strong, inducible T5 or T7 bacteriophage promoter may be used.

Yeast expression systems may be used for production of NuABP. A number of vectors containing constitutive or inducible promoters, such as alpha factor, alcohol oxidase, and PGH promoters, may be used in the yeast Saccharomyces cerevisiae or Pichia pastoris. In addition, such vectors direct either the secretion or intracellular retention of expressed proteins and enable integration of foreign sequences into the host genome for stable propagation. (See, e.g., Ausubel, 1995, supra; Bitter, G.A. et al. (1987) Methods Enzymol. 153:516-544; and Scorer, C.A. et al. (1994) Bio/Technology 12:181-184.)

Plant systems may also be used for expression of NuABP. Transcription of sequences encoding NuABP may be driven viral promoters, e.g., the 35S and 19S promoters of CaMV used alone or in combination with the omega leader sequence from TMV (Takamatsu, N. (1987) EMBO J. 6:307-311). Alternatively, plant promoters such as the small subunit of RUBISCO or heat shock promoters may be used. (See, e.g., Coruzzi, G. et al. (1984) EMBO J. 3:1671-1680; Broglie, R. et al.

(1984) Science 224:838-843; and Winter, J. et al. (1991) Results Probl. Cell Differ. 17:85-105.) These constructs can be introduced into plant cells by direct DNA transformation or pathogen-mediated transfection. (See, e.g., The McGraw Hill Yearbook of Science and Technology (1992) McGraw Hill, New York NY, pp. 191-196.)

In mammalian cells, a number of viral-based expression systems may be utilized. In cases where an adenovirus is used as an expression vector, sequences encoding NuABP may be ligated into an adenovirus transcription/translation complex consisting of the late promoter and tripartite leader sequence. Insertion in a non-essential E1 or E3 region of the viral genome may be used to obtain infective virus which expresses NuABP in host cells. (See, e.g., Logan, J. and T. Shenk (1984) Proc. Natl. Acad. Sci. USA 81:3655-3659.) In addition, transcription enhancers, such as the Rous sarcoma virus (RSV) enhancer, may be used to increase expression in mammalian host cells. SV40 or EBV-based vectors may also be used for high-level protein expression.

Human artificial chromosomes (HACs) may also be employed to deliver larger fragments of DNA than can be contained in and expressed from a plasmid. HACs of about 6 kb to 10 Mb are constructed and delivered via conventional delivery methods (liposomes, polycationic amino polymers, or vesicles) for therapeutic purposes. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355.)

For long term production of recombinant proteins in mammalian systems, stable expression of NuABP in cell lines is preferred. For example, sequences encoding NuABP can be transformed into cell lines using expression vectors which may contain viral origins of replication and/or endogenous expression elements and a selectable marker gene on the same or on a separate vector. Following the introduction of the vector, cells may be allowed to grow for about 1 to 2 days in enriched media before being switched to selective media. The purpose of the selectable marker is to confer resistance to a selective agent, and its presence allows growth and recovery of cells which successfully express the introduced sequences. Resistant clones of stably transformed cells may be propagated using tissue culture techniques appropriate to the cell type.

Any number of selection systems may be used to recover transformed cell lines. These include, but are not limited to, the herpes simplex virus thymidine kinase and adenine phosphoribosyltransferase genes, for use in *tk*$^-$ and *apr*$^-$ cells, respectively. (See, e.g., Wigler, M. et al. (1977) Cell 11:223-232; Lowy, I. et al. (1980) Cell 22:817-823.) Also, antimetabolite, antibiotic, or herbicide resistance can be used as the basis for selection. For example, *dhfr* confers resistance to methotrexate; *neo* confers resistance to the aminoglycosides neomycin and G-418; and *als* and *pat* confer resistance to chlorsulfuron and phosphinotricin acetyltransferase, respectively. (See, e.g., Wigler, M. et al. (1980) Proc. Natl. Acad. Sci. USA 77:3567-3570; Colbere-Garapin, F. et al. (1981) J. Mol. Biol. 150:1-14.) Additional selectable genes have been described, e.g., *trpB* and *hisD*, which

alter cellular requirements for metabolites. (See, e.g., Hartman, S.C. and R.C. Mulligan (1988) Proc. Natl. Acad. Sci. USA 85:8047-8051.) Visible markers, e.g., anthocyanins, green fluorescent proteins (GFP; Clontech), ß glucuronidase and its substrate ß-glucuronide, or luciferase and its substrate luciferin may be used. These markers can be used not only to identify transformants, but also to quantify the amount of transient or stable protein expression attributable to a specific vector system. (See, e.g., Rhodes, C.A. (1995) Methods Mol. Biol. 55:121-131.)

Although the presence/absence of marker gene expression suggests that the gene of interest is also present, the presence and expression of the gene may need to be confirmed. For example, if the sequence encoding NuABP is inserted within a marker gene sequence, transformed cells containing sequences encoding NuABP can be identified by the absence of marker gene function. Alternatively, a marker gene can be placed in tandem with a sequence encoding NuABP under the control of a single promoter. Expression of the marker gene in response to induction or selection usually indicates expression of the tandem gene as well.

In general, host cells that contain the nucleic acid sequence encoding NuABP and that express NuABP may be identified by a variety of procedures known to those of skill in the art. These procedures include, but are not limited to, DNA-DNA or DNA-RNA hybridizations, PCR amplification, and protein bioassay or immunoassay techniques which include membrane, solution, or chip based technologies for the detection and/or quantification of nucleic acid or protein sequences.

Immunological methods for detecting and measuring the expression of NuABP using either specific polyclonal or monoclonal antibodies are known in the art. Examples of such techniques include enzyme-linked immunosorbent assays (ELISAs), radioimmunoassays (RIAs), and fluorescence activated cell sorting (FACS). A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering epitopes on NuABP is preferred, but a competitive binding assay may be employed. These and other assays are well known in the art. (See, e.g., Hampton, R. et al. (1990) Serological Methods, a Laboratory Manual, APS Press, St. Paul MN, Sect. IV; Coligan, J.E. et al. (1997) Current Protocols in Immunology, Greene Pub. Associates and Wiley-Interscience, New York NY; and Pound, J.D. (1998) Immunochemical Protocols, Humana Press, Totowa NJ.)

A wide variety of labels and conjugation techniques are known by those skilled in the art and may be used in various nucleic acid and amino acid assays. Means for producing labeled hybridization or PCR probes for detecting sequences related to polynucleotides encoding NuABP include oligolabeling, nick translation, end-labeling, or PCR amplification using a labeled nucleotide. Alternatively, the sequences encoding NuABP, or any fragments thereof, may be cloned into a vector for the production of an mRNA probe. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by addition of an appropriate RNA polymerase

such as T7, T3, or SP6 and labeled nucleotides. These procedures may be conducted using a variety of commercially available kits, such as those provided by Amersham Pharmacia Biotech, Promega (Madison WI), and US Biochemical. Suitable reporter molecules or labels which may be used for ease of detection include radionuclides, enzymes, fluorescent, chemiluminescent, or chromogenic agents, as well as substrates, cofactors, inhibitors, magnetic particles, and the like.

Host cells transformed with nucleotide sequences encoding NuABP may be cultured under conditions suitable for the expression and recovery of the protein from cell culture. The protein produced by a transformed cell may be secreted or retained intracellularly depending on the sequence and/or the vector used. As will be understood by those of skill in the art, expression vectors containing polynucleotides which encode NuABP may be designed to contain signal sequences which direct secretion of NuABP through a prokaryotic or eukaryotic cell membrane.

In addition, a host cell strain may be chosen for its ability to modulate expression of the inserted sequences or to process the expressed protein in the desired fashion. Such modifications of the polypeptide include, but are not limited to, acetylation, carboxylation, glycosylation, phosphorylation, lipidation, and acylation. Post-translational processing which cleaves a "prepro" or "pro" form of the protein may also be used to specify protein targeting, folding, and/or activity. Different host cells which have specific cellular machinery and characteristic mechanisms for post-translational activities (e.g., CHO, HeLa, MDCK, HEK293, and WI38) are available from the American Type Culture Collection (ATCC, Manassas VA) and may be chosen to ensure the correct modification and processing of the foreign protein.

In another embodiment of the invention, natural, modified, or recombinant nucleic acid sequences encoding NuABP may be ligated to a heterologous sequence resulting in translation of a fusion protein in any of the aforementioned host systems. For example, a chimeric NuABP protein containing a heterologous moiety that can be recognized by a commercially available antibody may facilitate the screening of peptide libraries for inhibitors of NuABP activity. Heterologous protein and peptide moieties may also facilitate purification of fusion proteins using commercially available affinity matrices. Such moieties include, but are not limited to, glutathione S-transferase (GST), maltose binding protein (MBP), thioredoxin (Trx), calmodulin binding peptide (CBP), 6-His, FLAG, *c-myc*, and hemagglutinin (HA). GST, MBP, Trx, CBP, and 6-His enable purification of their cognate fusion proteins on immobilized glutathione, maltose, phenylarsine oxide, calmodulin, and metal-chelate resins, respectively. FLAG, *c-myc*, and hemagglutinin (HA) enable immunoaffinity purification of fusion proteins using commercially available monoclonal and polyclonal antibodies that specifically recognize these epitope tags. A fusion protein may also be engineered to contain a proteolytic cleavage site located between the NuABP encoding sequence and the heterologous protein sequence, so that NuABP may be cleaved away from the heterologous moiety following purification.

Methods for fusion protein expression and purification are discussed in Ausubel (1995, supra, ch. 10). A variety of commercially available kits may also be used to facilitate expression and purification of fusion proteins.

In a further embodiment of the invention, synthesis of radiolabeled NuABP may be achieved in vitro using the TNT rabbit reticulocyte lysate or wheat germ extract system (Promega). These systems couple transcription and translation of protein-coding sequences operably associated with the T7, T3, or SP6 promoters. Translation takes place in the presence of a radiolabeled amino acid precursor, for example, ^{35}S-methionine.

Fragments of NuABP may be produced not only by recombinant means, but also by direct peptide synthesis using solid-phase techniques. (See, e.g., Creighton, supra, pp. 55-60.) Protein synthesis may be performed by manual techniques or by automation. Automated synthesis may be achieved, for example, using the ABI 431A peptide synthesizer (Perkin-Elmer). Various fragments of NuABP may be synthesized separately and then combined to produce the full length molecule.

THERAPEUTICS

Chemical and structural similarity, e.g., in the context of sequences and motifs, exists between regions of NuABP and nucleic-acid binding proteins. In addition, the expression of NuABP is closely associated with proliferative, neuronal, inflamed, and cancerous tissues and tissues of the reproductive system. Therefore, NuABP appears to play a role in reproductive, immune, and neurological disorders, and cell proliferative disorders including cancer. In the treatment of disorders associated with increased NuABP expression or activity, it is desirable to decrease the expression or activity of NuABP. In the treatment of disorders associated with decreased NuABP expression or activity, it is desirable to increase the expression or activity of NuABP.

Therefore, in one embodiment, NuABP or a fragment or derivative thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of NuABP. Examples of such disorders include, but are not limited to, a reproductive disorder such as disorders of prolactin production, infertility, including tubal disease, ovulatory defects, and endometriosis, disruptions of the estrous cycle, disruptions of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, endometrial and ovarian tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the breast, fibrocystic breast disease, and galactorrhea; disruptions of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia; an immune disorder such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis,

cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis. Goodpasture's syndrome, gout, Graves' disease. Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; and a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus.

In another embodiment, a vector capable of expressing NuABP or a fragment or derivative

thereof may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of NuABP including, but not limited to, those described above.

In a further embodiment, a pharmaceutical composition comprising a substantially purified NuABP in conjunction with a suitable pharmaceutical carrier may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of NuABP including, but not limited to, those provided above.

In still another embodiment, an agonist which modulates the activity of NuABP may be administered to a subject to treat or prevent a disorder associated with decreased expression or activity of NuABP including, but not limited to, those listed above.

In a further embodiment, an antagonist of NuABP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of NuABP. Examples of such disorders include, but are not limited to, those reproductive, immune, and neurological disorders, and cell proliferative disorders including cancer, described above. In one aspect, an antibody which specifically binds NuABP may be used directly as an antagonist or indirectly as a targeting or delivery mechanism for bringing a pharmaceutical agent to cells or tissues which express NuABP.

In an additional embodiment, a vector expressing the complement of the polynucleotide encoding NuABP may be administered to a subject to treat or prevent a disorder associated with increased expression or activity of NuABP including, but not limited to, those described above.

In other embodiments, any of the proteins, antagonists, antibodies, agonists, complementary sequences, or vectors of the invention may be administered in combination with other appropriate therapeutic agents. Selection of the appropriate agents for use in combination therapy may be made by one of ordinary skill in the art, according to conventional pharmaceutical principles. The combination of therapeutic agents may act synergistically to effect the treatment or prevention of the various disorders described above. Using this approach, one may be able to achieve therapeutic efficacy with lower dosages of each agent, thus reducing the potential for adverse side effects.

An antagonist of NuABP may be produced using methods which are generally known in the art. In particular, purified NuABP may be used to produce antibodies or to screen libraries of pharmaceutical agents to identify those which specifically bind NuABP. Antibodies to NuABP may also be generated using methods that are well known in the art. Such antibodies may include, but are not limited to, polyclonal, monoclonal, chimeric, and single chain antibodies, Fab fragments, and fragments produced by a Fab expression library. Neutralizing antibodies (i.e., those which inhibit dimer formation) are generally preferred for therapeutic use.

For the production of antibodies, various hosts including goats, rabbits, rats, mice, humans, and others may be immunized by injection with NuABP or with any fragment or oligopeptide thereof which has immunogenic properties. Depending on the host species, various adjuvants may be used to

increase immunological response. Such adjuvants include, but are not limited to, Freund's, mineral gels such as aluminum hydroxide, and surface active substances such as lysolecithin, pluronic polyols, polyanions, peptides, oil emulsions, KLH, and dinitrophenol. Among adjuvants used in humans, BCG (bacilli Calmette-Guerin) and Corynebacterium parvum are especially preferable.

It is preferred that the oligopeptides, peptides, or fragments used to induce antibodies to NuABP have an amino acid sequence consisting of at least about 5 amino acids, and generally will consist of at least about 10 amino acids. It is also preferable that these oligopeptides, peptides, or fragments are identical to a portion of the amino acid sequence of the natural protein and contain the entire amino acid sequence of a small, naturally occurring molecule. Short stretches of NuABP amino acids may be fused with those of another protein, such as KLH, and antibodies to the chimeric molecule may be produced.

Monoclonal antibodies to NuABP may be prepared using any technique which provides for the production of antibody molecules by continuous cell lines in culture. These include, but are not limited to, the hybridoma technique, the human B-cell hybridoma technique, and the EBV-hybridoma technique. (See, e.g., Kohler, G. et al. (1975) Nature 256:495-497; Kozbor, D. et al. (1985) J. Immunol. Methods 81:31-42; Cote, R.J. et al. (1983) Proc. Natl. Acad. Sci. USA 80:2026-2030; and Cole, S.P. et al. (1984) Mol. Cell Biol. 62:109-120.)

In addition, techniques developed for the production of "chimeric antibodies," such as the splicing of mouse antibody genes to human antibody genes to obtain a molecule with appropriate antigen specificity and biological activity, can be used. (See, e.g., Morrison, S.L. et al. (1984) Proc. Natl. Acad. Sci. USA 81:6851-6855; Neuberger, M.S. et al. (1984) Nature 312:604-608; and Takeda, S. et al. (1985) Nature 314:452-454.) Alternatively, techniques described for the production of single chain antibodies may be adapted, using methods known in the art, to produce NuABP-specific single chain antibodies. Antibodies with related specificity, but of distinct idiotypic composition, may be generated by chain shuffling from random combinatorial immunoglobulin libraries. (See, e.g., Burton, D.R. (1991) Proc. Natl. Acad. Sci. USA 88:10134-10137.)

Antibodies may also be produced by inducing in vivo production in the lymphocyte population or by screening immunoglobulin libraries or panels of highly specific binding reagents as disclosed in the literature. (See, e.g., Orlandi, R. et al. (1989) Proc. Natl. Acad. Sci. USA 86:3833-3837; Winter, G. et al. (1991) Nature 349:293-299.)

Antibody fragments which contain specific binding sites for NuABP may also be generated. For example, such fragments include, but are not limited to, $F(ab')_2$ fragments produced by pepsin digestion of the antibody molecule and Fab fragments generated by reducing the disulfide bridges of the F(ab')2 fragments. Alternatively, Fab expression libraries may be constructed to allow rapid and easy identification of monoclonal Fab fragments with the desired specificity. (See, e.g., Huse, W.D.

et al. (1989) Science 246:1275-1281.)

Various immunoassays may be used for screening to identify antibodies having the desired specificity. Numerous protocols for competitive binding or immunoradiometric assays using either polyclonal or monoclonal antibodies with established specificities are well known in the art. Such immunoassays typically involve the measurement of complex formation between NuABP and its specific antibody. A two-site, monoclonal-based immunoassay utilizing monoclonal antibodies reactive to two non-interfering NuABP epitopes is generally used, but a competitive binding assay may also be employed (Pound, supra).

Various methods such as Scatchard analysis in conjunction with radioimmunoassay techniques may be used to assess the affinity of antibodies for NuABP. Affinity is expressed as an association constant, K_a, which is defined as the molar concentration of NuABP-antibody complex divided by the molar concentrations of free antigen and free antibody under equilibrium conditions. The K_a determined for a preparation of polyclonal antibodies, which are heterogeneous in their affinities for multiple NuABP epitopes, represents the average affinity, or avidity, of the antibodies for NuABP. The K_a determined for a preparation of monoclonal antibodies, which are monospecific for a particular NuABP epitope, represents a true measure of affinity. High-affinity antibody preparations with K_a ranging from about 10^9 to 10^{12} L/mole are preferred for use in immunoassays in which the NuABP-antibody complex must withstand rigorous manipulations. Low-affinity antibody preparations with K_a ranging from about 10^6 to 10^7 L/mole are preferred for use in immunopurification and similar procedures which ultimately require dissociation of NuABP, preferably in active form, from the antibody (Catty, D. (1988) Antibodies, Volume I: A Practical Approach, IRL Press, Washington, DC; Liddell, J.E. and Cryer, A. (1991) A Practical Guide to Monoclonal Antibodies, John Wiley & Sons, New York NY).

The titer and avidity of polyclonal antibody preparations may be further evaluated to determine the quality and suitability of such preparations for certain downstream applications. For example, a polyclonal antibody preparation containing at least 1-2 mg specific antibody/ml, preferably 5-10 mg specific antibody/ml, is generally employed in procedures requiring precipitation of NuABP-antibody complexes. Procedures for evaluating antibody specificity, titer, and avidity, and guidelines for antibody quality and usage in various applications, are generally available. (See, e.g., Catty, supra, and Coligan et al. supra.)

In another embodiment of the invention, the polynucleotides encoding NuABP, or any fragment or complement thereof, may be used for therapeutic purposes. In one aspect, the complement of the polynucleotide encoding NuABP may be used in situations in which it would be desirable to block the transcription of the mRNA. In particular, cells may be transformed with sequences complementary to polynucleotides encoding NuABP. Thus, complementary molecules or

fragments may be used to modulate NuABP activity, or to achieve regulation of gene function. Such technology is now well known in the art, and sense or antisense oligonucleotides or larger fragments can be designed from various locations along the coding or control regions of sequences encoding NuABP.

Expression vectors derived from retroviruses, adenoviruses, or herpes or vaccinia viruses, or from various bacterial plasmids, may be used for delivery of nucleotide sequences to the targeted organ, tissue, or cell population. Methods which are well known to those skilled in the art can be used to construct vectors to express nucleic acid sequences complementary to the polynucleotides encoding NuABP. (See, e.g., Sambrook, supra; Ausubel, 1995, supra.)

Genes encoding NuABP can be turned off by transforming a cell or tissue with expression vectors which express high levels of a polynucleotide, or fragment thereof, encoding NuABP. Such constructs may be used to introduce untranslatable sense or antisense sequences into a cell. Even in the absence of integration into the DNA, such vectors may continue to transcribe RNA molecules until they are disabled by endogenous nucleases. Transient expression may last for a month or more with a non-replicating vector, and may last even longer if appropriate replication elements are part of the vector system.

As mentioned above, modifications of gene expression can be obtained by designing complementary sequences or antisense molecules (DNA, RNA, or PNA) to the control, 5', or regulatory regions of the gene encoding NuABP. Oligonucleotides derived from the transcription initiation site, e.g., between about positions -10 and +10 from the start site, may be employed. Similarly, inhibition can be achieved using triple helix base-pairing methodology. Triple helix pairing is useful because it causes inhibition of the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors, or regulatory molecules. Recent therapeutic advances using triplex DNA have been described in the literature. (See, e.g., Gee, J.E. et al. (1994) in Huber, B.E. and B.I. Carr, Molecular and Immunologic Approaches, Futura Publishing, Mt. Kisco NY, pp. 163-177.) A complementary sequence or antisense molecule may also be designed to block translation of mRNA by preventing the transcript from binding to ribosomes.

Ribozymes, enzymatic RNA molecules, may also be used to catalyze the specific cleavage of RNA. The mechanism of ribozyme action involves sequence-specific hybridization of the ribozyme molecule to complementary target RNA, followed by endonucleolytic cleavage. For example, engineered hammerhead motif ribozyme molecules may specifically and efficiently catalyze endonucleolytic cleavage of sequences encoding NuABP.

Specific ribozyme cleavage sites within any potential RNA target are initially identified by scanning the target molecule for ribozyme cleavage sites, including the following sequences: GUA, GUU, and GUC. Once identified, short RNA sequences of between 15 and 20 ribonucleotides,

corresponding to the region of the target gene containing the cleavage site, may be evaluated for secondary structural features which may render the oligonucleotide inoperable. The suitability of candidate targets may also be evaluated by testing accessibility to hybridization with complementary oligonucleotides using ribonuclease protection assays.

Complementary ribonucleic acid molecules and ribozymes of the invention may be prepared by any method known in the art for the synthesis of nucleic acid molecules. These include techniques for chemically synthesizing oligonucleotides such as solid phase phosphoramidite chemical synthesis. Alternatively, RNA molecules may be generated by in vitro and in vivo transcription of DNA sequences encoding NuABP. Such DNA sequences may be incorporated into a wide variety of vectors with suitable RNA polymerase promoters such as T7 or SP6. Alternatively, these cDNA constructs that synthesize complementary RNA, constitutively or inducibly, can be introduced into cell lines, cells, or tissues.

RNA molecules may be modified to increase intracellular stability and half-life. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends of the molecule, or the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages within the backbone of the molecule. This concept is inherent in the production of PNAs and can be extended in all of these molecules by the inclusion of nontraditional bases such as inosine, queosine, and wybutosine, as well as acetyl-, methyl-, thio-, and similarly modified forms of adenine, cytidine, guanine, thymine, and uridine which are not as easily recognized by endogenous endonucleases.

Many methods for introducing vectors into cells or tissues are available and equally suitable for use in vivo, in vitro, and ex vivo. For ex vivo therapy, vectors may be introduced into stem cells taken from the patient and clonally propagated for autologous transplant back into that same patient. Delivery by transfection, by liposome injections, or by polycationic amino polymers may be achieved using methods which are well known in the art. (See, e.g., Goldman, C.K. et al. (1997) Nat. Biotechnol. 15:462-466.)

Any of the therapeutic methods described above may be applied to any subject in need of such therapy, including, for example, mammals such as humans, dogs, cats, cows, horses, rabbits, and monkeys.

An additional embodiment of the invention relates to the administration of a pharmaceutical or sterile composition, in conjunction with a pharmaceutically acceptable carrier, for any of the therapeutic effects discussed above. Such pharmaceutical compositions may consist of NuABP, antibodies to NuABP, and mimetics, agonists, antagonists, or inhibitors of NuABP. The compositions may be administered alone or in combination with at least one other agent, such as a stabilizing compound, which may be administered in any sterile, biocompatible pharmaceutical carrier including, but not limited to, saline, buffered saline, dextrose, and water. The compositions may be administered

to a patient alone, or in combination with other agents, drugs, or hormones.

The pharmaceutical compositions utilized in this invention may be administered by any number of routes including, but not limited to, oral, intravenous, intramuscular, intra-arterial, intramedullary, intrathecal, intraventricular, transdermal, subcutaneous, intraperitoneal, intranasal, enteral, topical, sublingual, or rectal means.

In addition to the active ingredients, these pharmaceutical compositions may contain suitable pharmaceutically-acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds into preparations which can be used pharmaceutically. Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing, Easton PA).

Pharmaceutical compositions for oral administration can be formulated using pharmaceutically acceptable carriers well known in the art in dosages suitable for oral administration. Such carriers enable the pharmaceutical compositions to be formulated as tablets, pills, dragees, capsules, liquids, gels, syrups, slurries, suspensions, and the like, for ingestion by the patient.

Pharmaceutical preparations for oral use can be obtained through combining active compounds with solid excipient and processing the resultant mixture of granules (optionally, after grinding) to obtain tablets or dragee cores. Suitable auxiliaries can be added, if desired. Suitable excipients include carbohydrate or protein fillers, such as sugars, including lactose, sucrose, mannitol, and sorbitol; starch from corn, wheat, rice, potato, or other plants; cellulose, such as methyl cellulose, hydroxypropylmethyl-cellulose, or sodium carboxymethylcellulose; gums, including arabic and tragacanth; and proteins, such as gelatin and collagen. If desired, disintegrating or solubilizing agents may be added, such as the cross-linked polyvinyl pyrrolidone, agar, and alginic acid or a salt thereof, such as sodium alginate.

Dragee cores may be used in conjunction with suitable coatings, such as concentrated sugar solutions, which may also contain gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs or pigments may be added to the tablets or dragee coatings for product identification or to characterize the quantity of active compound, i.e., dosage.

Pharmaceutical preparations which can be used orally include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a coating, such as glycerol or sorbitol. Push-fit capsules can contain active ingredients mixed with fillers or binders, such as lactose or starches, lubricants, such as talc or magnesium stearate, and, optionally, stabilizers. In soft capsules, the active compounds may be dissolved or suspended in suitable liquids, such as fatty oils, liquid, or liquid polyethylene glycol with or without stabilizers.

Pharmaceutical formulations suitable for parenteral administration may be formulated in

aqueous solutions, preferably in physiologically compatible buffers such as Hanks' solution, Ringer's solution, or physiologically buffered saline. Aqueous injection suspensions may contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Additionally, suspensions of the active compounds may be prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles include fatty oils, such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate, triglycerides, or liposomes. Non-lipid polycationic amino polymers may also be used for delivery. Optionally, the suspension may also contain suitable stabilizers or agents to increase the solubility of the compounds and allow for the preparation of highly concentrated solutions.

For topical or nasal administration, penetrants appropriate to the particular barrier to be permeated are used in the formulation. Such penetrants are generally known in the art.

The pharmaceutical compositions of the present invention may be manufactured in a manner that is known in the art, e.g., by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping, or lyophilizing processes.

The pharmaceutical composition may be provided as a salt and can be formed with many acids, including but not limited to, hydrochloric, sulfuric, acetic, lactic, tartaric, malic, and succinic acids. Salts tend to be more soluble in aqueous or other protonic solvents than are the corresponding free base forms. In other cases, the preparation may be a lyophilized powder which may contain any or all of the following: 1 mM to 50 mM histidine, 0.1% to 2% sucrose, and 2% to 7% mannitol, at a pH range of 4.5 to 5.5, that is combined with buffer prior to use.

After pharmaceutical compositions have been prepared, they can be placed in an appropriate container and labeled for treatment of an indicated condition. For administration of NuABP, such labeling would include amount, frequency, and method of administration.

Pharmaceutical compositions suitable for use in the invention include compositions wherein the active ingredients are contained in an effective amount to achieve the intended purpose. The determination of an effective dose is well within the capability of those skilled in the art.

For any compound, the therapeutically effective dose can be estimated initially either in cell culture assays, e.g., of neoplastic cells, or in animal models such as mice, rats, rabbits, dogs, or pigs. An animal model may also be used to determine the appropriate concentration range and route of administration. Such information can then be used to determine useful doses and routes for administration in humans.

A therapeutically effective dose refers to that amount of active ingredient, for example NuABP or fragments thereof, antibodies of NuABP, and agonists, antagonists or inhibitors of NuABP, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity may be determined by standard pharmaceutical procedures in cell cultures or with experimental animals, such

as by calculating the ED_{50} (the dose therapeutically effective in 50% of the population) or LD_{50} (the dose lethal to 50% of the population) statistics. The dose ratio of toxic to therapeutic effects is the therapeutic index, which can be expressed as the LD_{50}/ED_{50} ratio. Pharmaceutical compositions which exhibit large therapeutic indices are preferred. The data obtained from cell culture assays and animal studies are used to formulate a range of dosage for human use. The dosage contained in such compositions is preferably within a range of circulating concentrations that includes the ED_{50} with little or no toxicity. The dosage varies within this range depending upon the dosage form employed, the sensitivity of the patient, and the route of administration.

The exact dosage will be determined by the practitioner, in light of factors related to the subject requiring treatment. Dosage and administration are adjusted to provide sufficient levels of the active moiety or to maintain the desired effect. Factors which may be taken into account include the severity of the disease state, the general health of the subject, the age, weight, and gender of the subject, time and frequency of administration, drug combination(s), reaction sensitivities, and response to therapy. Long-acting pharmaceutical compositions may be administered every 3 to 4 days, every week, or biweekly depending on the half-life and clearance rate of the particular formulation.

Normal dosage amounts may vary from about 0.1 μg to 100,000 μg, up to a total dose of about 1 gram, depending upon the route of administration. Guidance as to particular dosages and methods of delivery is provided in the literature and generally available to practitioners in the art. Those skilled in the art will employ different formulations for nucleotides than for proteins or their inhibitors. Similarly, delivery of polynucleotides or polypeptides will be specific to particular cells, conditions, locations, etc.

DIAGNOSTICS

In another embodiment, antibodies which specifically bind NuABP may be used for the diagnosis of disorders characterized by expression of NuABP, or in assays to monitor patients being treated with NuABP or agonists, antagonists, or inhibitors of NuABP. Antibodies useful for diagnostic purposes may be prepared in the same manner as described above for therapeutics. Diagnostic assays for NuABP include methods which utilize the antibody and a label to detect NuABP in human body fluids or in extracts of cells or tissues. The antibodies may be used with or without modification, and may be labeled by covalent or non-covalent attachment of a reporter molecule. A wide variety of reporter molecules, several of which are described above, are known in the art and may be used.

A variety of protocols for measuring NuABP, including ELISAs, RIAs, and FACS, are known in the art and provide a basis for diagnosing altered or abnormal levels of NuABP expression. Normal or standard values for NuABP expression are established by combining body fluids or cell

extracts taken from normal mammalian subjects, for example, human subjects, with antibody to NuABP under conditions suitable for complex formation. The amount of standard complex formation may be quantitated by various methods, such as photometric means. Quantities of NuABP expressed in subject, control, and disease samples from biopsied tissues are compared with the standard values. Deviation between standard and subject values establishes the parameters for diagnosing disease.

In another embodiment of the invention, the polynucleotides encoding NuABP may be used for diagnostic purposes. The polynucleotides which may be used include oligonucleotide sequences, complementary RNA and DNA molecules, and PNAs. The polynucleotides may be used to detect and quantify gene expression in biopsied tissues in which expression of NuABP may be correlated with disease. The diagnostic assay may be used to determine absence, presence, and excess expression of NuABP, and to monitor regulation of NuABP levels during therapeutic intervention.

In one aspect, hybridization with PCR probes which are capable of detecting polynucleotide sequences, including genomic sequences, encoding NuABP or closely related molecules may be used to identify nucleic acid sequences which encode NuABP. The specificity of the probe, whether it is made from a highly specific region, e.g., the 5' regulatory region, or from a less specific region, e.g., a conserved motif, and the stringency of the hybridization or amplification will determine whether the probe identifies only naturally occurring sequences encoding NuABP, allelic variants, or related sequences.

Probes may also be used for the detection of related sequences, and may have at least 50% sequence identity to any of the NuABP encoding sequences. The hybridization probes of the subject invention may be DNA or RNA and may be derived from the sequence of SEQ ID NO:56-110 or from genomic sequences including promoters, enhancers, and introns of the NuABP gene.

Means for producing specific hybridization probes for DNAs encoding NuABP include the cloning of polynucleotide sequences encoding NuABP or NuABP derivatives into vectors for the production of mRNA probes. Such vectors are known in the art, are commercially available, and may be used to synthesize RNA probes in vitro by means of the addition of the appropriate RNA polymerases and the appropriate labeled nucleotides. Hybridization probes may be labeled by a variety of reporter groups, for example, by radionuclides such as ^{32}P or ^{35}S, or by enzymatic labels, such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems, and the like.

Polynucleotide sequences encoding NuABP may be used for the diagnosis of disorders associated with expression of NuABP. Examples of such disorders include, but are not limited to, a reproductive disorder such as disorders of prolactin production, infertility, including tubal disease, ovulatory defects, and endometriosis, disruptions of the estrous cycle, disruptions of the menstrual cycle, polycystic ovary syndrome, ovarian hyperstimulation syndrome, endometrial and ovarian tumors, uterine fibroids, autoimmune disorders, ectopic pregnancies, and teratogenesis; cancer of the

breast, fibrocystic breast disease, and galactorrhea; disruptions of spermatogenesis, abnormal sperm physiology, cancer of the testis, cancer of the prostate, benign prostatic hyperplasia, prostatitis, Peyronie's disease, impotence, carcinoma of the male breast, and gynecomastia; an immune disorder such as inflammation, actinic keratosis, acquired immunodeficiency syndrome (AIDS), Addison's disease, adult respiratory distress syndrome, allergies, ankylosing spondylitis, amyloidosis, anemia, arteriosclerosis, asthma, atherosclerosis, autoimmune hemolytic anemia, autoimmune thyroiditis, bronchitis, bursitis, cholecystitis, cirrhosis, contact dermatitis, Crohn's disease, atopic dermatitis, dermatomyositis, diabetes mellitus, emphysema, erythroblastosis fetalis, erythema nodosum, atrophic gastritis, glomerulonephritis, Goodpasture's syndrome, gout, Graves' disease, Hashimoto's thyroiditis, paroxysmal nocturnal hemoglobinuria, hepatitis, hypereosinophilia, irritable bowel syndrome, episodic lymphopenia with lymphocytotoxins, mixed connective tissue disease (MCTD), multiple sclerosis, myasthenia gravis, myocardial or pericardial inflammation, myelofibrosis, osteoarthritis, osteoporosis, pancreatitis, polycythemia vera, polymyositis, psoriasis, Reiter's syndrome, rheumatoid arthritis, scleroderma, Sjögren's syndrome, systemic anaphylaxis, systemic lupus erythematosus, systemic sclerosis, primary thrombocythemia, thrombocytopenic purpura, ulcerative colitis, uveitis, Werner syndrome, complications of cancer, hemodialysis, and extracorporeal circulation, trauma, and hematopoietic cancer including lymphoma, leukemia, and myeloma; a neurological disorder such as epilepsy, ischemic cerebrovascular disease, stroke, cerebral neoplasms, Alzheimer's disease, Pick's disease, Huntington's disease, dementia, Parkinson's disease and other extrapyramidal disorders, amyotrophic lateral sclerosis and other motor neuron disorders, progressive neural muscular atrophy, retinitis pigmentosa, hereditary ataxias, multiple sclerosis and other demyelinating diseases, bacterial and viral meningitis, brain abscess, subdural empyema, epidural abscess, suppurative intracranial thrombophlebitis, myelitis and radiculitis, viral central nervous system disease, prion diseases including kuru, Creutzfeldt-Jakob disease, and Gerstmann-Straussler-Scheinker syndrome, fatal familial insomnia, nutritional and metabolic diseases of the nervous system, neurofibromatosis, tuberous sclerosis, cerebelloretinal hemangioblastomatosis, encephalotrigeminal syndrome, mental retardation and other developmental disorders of the central nervous system, cerebral palsy, neuroskeletal disorders, autonomic nervous system disorders, cranial nerve disorders, spinal cord diseases, muscular dystrophy and other neuromuscular disorders, peripheral nervous system disorders, dermatomyositis and polymyositis, inherited, metabolic, endocrine, and toxic myopathies, myasthenia gravis, periodic paralysis, mental disorders including mood, anxiety, and schizophrenic disorders, akathesia, amnesia, catatonia, diabetic neuropathy, tardive dyskinesia, dystonias, paranoid psychoses, postherpetic neuralgia, and Tourette's disorder; and a cell proliferative disorder such as actinic keratosis, arteriosclerosis, atherosclerosis, bursitis, cirrhosis, hepatitis, mixed connective tissue disease (MCTD), myelofibrosis, paroxysmal nocturnal

hemoglobinuria, polycythemia vera, psoriasis, primary thrombocythemia, and cancers including adenocarcinoma, leukemia, lymphoma, melanoma, myeloma, sarcoma, teratocarcinoma, and, in particular, cancers of the adrenal gland, bladder, bone, bone marrow, brain, breast, cervix, gall bladder, ganglia, gastrointestinal tract, heart, kidney, liver, lung, muscle, ovary, pancreas, parathyroid, penis, prostate, salivary glands, skin, spleen, testis, thymus, thyroid, and uterus. The polynucleotide sequences encoding NuABP may be used in Southern or northern analysis, dot blot, or other membrane-based technologies; in PCR technologies; in dipstick, pin, and multiformat ELISA-like assays; and in microarrays utilizing fluids or tissues from patients to detect altered NuABP expression. Such qualitative or quantitative methods are well known in the art.

In a particular aspect, the nucleotide sequences encoding NuABP may be useful in assays that detect the presence of associated disorders, particularly those mentioned above. The nucleotide sequences encoding NuABP may be labeled by standard methods and added to a fluid or tissue sample from a patient under conditions suitable for the formation of hybridization complexes. After a suitable incubation period, the sample is washed and the signal is quantified and compared with a standard value. If the amount of signal in the patient sample is significantly altered in comparison to a control sample then the presence of altered levels of nucleotide sequences encoding NuABP in the sample indicates the presence of the associated disorder. Such assays may also be used to evaluate the efficacy of a particular therapeutic treatment regimen in animal studies, in clinical trials, or to monitor the treatment of an individual patient.

In order to provide a basis for the diagnosis of a disorder associated with expression of NuABP, a normal or standard profile for expression is established. This may be accomplished by combining body fluids or cell extracts taken from normal subjects, either animal or human, with a sequence, or a fragment thereof, encoding NuABP, under conditions suitable for hybridization or amplification. Standard hybridization may be quantified by comparing the values obtained from normal subjects with values from an experiment in which a known amount of a substantially purified polynucleotide is used. Standard values obtained in this manner may be compared with values obtained from samples from patients who are symptomatic for a disorder. Deviation from standard values is used to establish the presence of a disorder.

Once the presence of a disorder is established and a treatment protocol is initiated, hybridization assays may be repeated on a regular basis to determine if the level of expression in the patient begins to approximate that which is observed in the normal subject. The results obtained from successive assays may be used to show the efficacy of treatment over a period ranging from several days to months.

With respect to cancer, the presence of an abnormal amount of transcript (either under- or overexpressed) in biopsied tissue from an individual may indicate a predisposition for the

development of the disease, or may provide a means for detecting the disease prior to the appearance of actual clinical symptoms. A more definitive diagnosis of this type may allow health professionals to employ preventative measures or aggressive treatment earlier thereby preventing the development or further progression of the cancer.

Additional diagnostic uses for oligonucleotides designed from the sequences encoding NuABP may involve the use of PCR. These oligomers may be chemically synthesized, generated enzymatically, or produced in vitro. Oligomers will preferably contain a fragment of a polynucleotide encoding NuABP, or a fragment of a polynucleotide complementary to the polynucleotide encoding NuABP, and will be employed under optimized conditions for identification of a specific gene or condition. Oligomers may also be employed under less stringent conditions for detection or quantification of closely related DNA or RNA sequences.

Methods which may also be used to quantify the expression of NuABP include radiolabeling or biotinylating nucleotides, coamplification of a control nucleic acid, and interpolating results from standard curves. (See, e.g., Melby, P.C. et al. (1993) J. Immunol. Methods 159:235-244; Duplaa, C. et al. (1993) Anal. Biochem. 212:229-236.) The speed of quantitation of multiple samples may be accelerated by running the assay in a high-throughput format where the oligomer of interest is presented in various dilutions and a spectrophotometric or colorimetric response gives rapid quantitation.

In further embodiments, oligonucleotides or longer fragments derived from any of the polynucleotide sequences described herein may be used as targets in a microarray. The microarray can be used to monitor the expression level of large numbers of genes simultaneously and to identify genetic variants, mutations, and polymorphisms. This information may be used to determine gene function, to understand the genetic basis of a disorder, to diagnose a disorder, and to develop and monitor the activities of therapeutic agents.

Microarrays may be prepared, used, and analyzed using methods known in the art. (See, e.g., Brennan, T.M. et al. (1995) U.S. Patent No. 5,474,796; Schena, M. et al. (1996) Proc. Natl. Acad. Sci. USA 93:10614-10619; Baldeschweiler et al. (1995) PCT application WO95/251116; Shalon, D. et al. (1995) PCT application WO95/35505; Heller, R.A. et al. (1997) Proc. Natl. Acad. Sci. USA 94:2150-2155; and Heller, M.J. et al. (1997) U.S. Patent No. 5,605,662.)

In another embodiment of the invention, nucleic acid sequences encoding NuABP may be used to generate hybridization probes useful in mapping the naturally occurring genomic sequence. The sequences may be mapped to a particular chromosome, to a specific region of a chromosome, or to artificial chromosome constructions, e.g., human artificial chromosomes (HACs), yeast artificial chromosomes (YACs), bacterial artificial chromosomes (BACs), bacterial P1 constructions, or single chromosome cDNA libraries. (See, e.g., Harrington, J.J. et al. (1997) Nat. Genet. 15:345-355; Price,

C.M. (1993) Blood Rev. 7:127-134; and Trask, B.J. (1991) Trends Genet. 7:149-154.)

Fluorescent in situ hybridization (FISH) may be correlated with other physical chromosome mapping techniques and genetic map data. (See, e.g., Heinz-Ulrich, et al. (1995) in Meyers, supra, pp. 965-968.) Examples of genetic map data can be found in various scientific journals or at the Online Mendelian Inheritance in Man (OMIM) World Wide Web site. Correlation between the location of the gene encoding NuABP on a physical chromosomal map and a specific disorder, or a predisposition to a specific disorder, may help define the region of DNA associated with that disorder. The nucleotide sequences of the invention may be used to detect differences in gene sequences among normal, carrier, and affected individuals.

In situ hybridization of chromosomal preparations and physical mapping techniques, such as linkage analysis using established chromosomal markers, may be used for extending genetic maps. Often the placement of a gene on the chromosome of another mammalian species, such as mouse, may reveal associated markers even if the number or arm of a particular human chromosome is not known. New sequences can be assigned to chromosomal arms by physical mapping. This provides valuable information to investigators searching for disease genes using positional cloning or other gene discovery techniques. Once the disease or syndrome has been crudely localized by genetic linkage to a particular genomic region, e.g., ataxia-telangiectasia to 11q22-23, any sequences mapping to that area may represent associated or regulatory genes for further investigation. (See, e.g., Gatti, R.A. et al. (1988) Nature 336:577-580.) The nucleotide sequence of the subject invention may also be used to detect differences in the chromosomal location due to translocation, inversion, etc., among normal, carrier, or affected individuals.

In another embodiment of the invention, NuABP, its catalytic or immunogenic fragments, or oligopeptides thereof can be used for screening libraries of compounds in any of a variety of drug screening techniques. The fragment employed in such screening may be free in solution, affixed to a solid support, borne on a cell surface, or located intracellularly. The formation of binding complexes between NuABP and the agent being tested may be measured.

Another technique for drug screening provides for high throughput screening of compounds having suitable binding affinity to the protein of interest. (See, e.g., Geysen, et al. (1984) PCT application WO84/03564.) In this method, large numbers of different small test compounds are synthesized on a solid substrate. The test compounds are reacted with NuABP, or fragments thereof, and washed. Bound NuABP is then detected by methods well known in the art. Purified NuABP can also be coated directly onto plates for use in the aforementioned drug screening techniques. Alternatively, non-neutralizing antibodies can be used to capture the peptide and immobilize it on a solid support.

In another embodiment, one may use competitive drug screening assays in which neutralizing

antibodies capable of binding NuABP specifically compete with a test compound for binding NuABP. In this manner, antibodies can be used to detect the presence of any peptide which shares one or more antigenic determinants with NuABP.

In additional embodiments, the nucleotide sequences which encode NuABP may be used in any molecular biology techniques that have yet to be developed, provided the new techniques rely on properties of nucleotide sequences that are currently known, including, but not limited to, such properties as the triplet genetic code and specific base pair interactions.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

Without further elaboration, it is believed that one skilled in the art can, using the preceding description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The disclosures of all patents, applications, and publications mentioned above and below, in particular U.S. Ser. No. 60/117,905 and U.S. Ser. No. 60/117,904, are hereby expressly incorporated by reference.

EXAMPLES

I. Construction of cDNA Libraries

RNA was purchased from Clontech or isolated from tissues described in Table 4. Some tissues were homogenized and lysed in guanidinium isothiocyanate, while others were homogenized and lysed in phenol or in a suitable mixture of denaturants, such as TRIZOL (Life Technologies), a monophasic solution of phenol and guanidine isothiocyanate. The resulting lysates were centrifuged over CsCl cushions or extracted with chloroform. RNA was precipitated from the lysates with either isopropanol or sodium acetate and ethanol, or by other routine methods.

Phenol extraction and precipitation of RNA were repeated as necessary to increase RNA purity. In some cases, RNA was treated with DNase. For most libraries, poly(A+) RNA was isolated using oligo d(T)-coupled paramagnetic particles (Promega), OLIGOTEX latex particles (QIAGEN, Chatsworth CA), or an OLIGOTEX mRNA purification kit (QIAGEN). Alternatively, RNA was isolated directly from tissue lysates using other RNA isolation kits, e.g., the POLY(A)PURE mRNA purification kit (Ambion, Austin TX).

In some cases, Stratagene was provided with RNA and constructed the corresponding cDNA libraries. Otherwise, cDNA was synthesized and cDNA libraries were constructed with the UNIZAP

vector system (Stratagene) or SUPERSCRIPT plasmid system (Life Technologies), using the recommended procedures or similar methods known in the art. (See, e.g., Ausubel, 1997, supra, units 5.1-6.6.) Reverse transcription was initiated using oligo d(T) or random primers. Synthetic oligonucleotide adapters were ligated to double stranded cDNA, and the cDNA was digested with the appropriate restriction enzyme or enzymes. For most libraries, the cDNA was size-selected (300-1000 bp) using SEPHACRYL S1000, SEPHAROSE CL2B, or SEPHAROSE CL4B column chromatography (Amersham Pharmacia Biotech) or preparative agarose gel electrophoresis. cDNAs were ligated into compatible restriction enzyme sites of the polylinker of a suitable plasmid, e.g., PBLUESCRIPT plasmid (Stratagene), PSPORT1 plasmid (Life Technologies), or pINCY (Incyte Pharmaceuticals, Palo Alto CA). Recombinant plasmids were transformed into competent E. coli cells including XL1-Blue, XL1-BlueMRF, or SOLR from Stratagene or DH5α, DH10B, or ElectroMAX DH10B from Life Technologies.

II. Isolation of cDNA Clones

Plasmids were recovered from host cells by in vivo excision using the UNIZAP vector system (Stratagene) or by cell lysis. Plasmids were purified using at least one of the following: a Magic or WIZARD Minipreps DNA purification system (Promega); an AGTC Miniprep purification kit (Edge Biosystems, Gaithersburg MD); and QIAWELL 8 Plasmid, QIAWELL 8 Plus Plasmid, QIAWELL 8 Ultra Plasmid purification systems or the R.E.A.L. PREP 96 plasmid purification kit from QIAGEN. Following precipitation, plasmids were resuspended in 0.1 ml of distilled water and stored, with or without lyophilization, at 4°C.

Alternatively, plasmid DNA was amplified from host cell lysates using direct link PCR in a high-throughput format (Rao, V.B. (1994) Anal. Biochem. 216:1-14). Host cell lysis and thermal cycling steps were carried out in a single reaction mixture. Samples were processed and stored in 384-well plates, and the concentration of amplified plasmid DNA was quantified fluorometrically using PICOGREEN dye (Molecular Probes, Eugene OR) and a FLUOROSKAN II fluorescence scanner (Labsystems Oy, Helsinki, Finland).

III. Sequencing and Analysis

cDNA sequencing reactions were processed using standard methods or high-throughput instrumentation such as the ABI CATALYST 800 (Perkin-Elmer) thermal cycler or the PTC-200 thermal cycler (MJ Research) in conjunction with the HYDRA microdispenser (Robbins Scientific) or the MICROLAB 2200 (Hamilton) liquid transfer system. cDNA sequencing reactions were prepared using reagents provided by Amersham Pharmacia Biotech or supplied in ABI sequencing kits such as the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer). Electrophoretic separation of cDNA sequencing reactions and detection of labeled polynucleotides were carried out using the MEGABACE 1000 DNA sequencing system (Molecular Dynamics); the

ABI PRISM 373 or 377 sequencing system (Perkin-Elmer) in conjunction with standard ABI protocols and base calling software; or other sequence analysis systems known in the art. Reading frames within the cDNA sequences were identified using standard methods (reviewed in Ausubel, 1997, supra, unit 7.7). Some of the cDNA sequences were selected for extension using the techniques disclosed in Example V.

The polynucleotide sequences derived from cDNA sequencing were assembled and analyzed using a combination of software programs which utilize algorithms well known to those skilled in the art. Table 5 summarizes the tools, programs, and algorithms used and provides applicable descriptions, references, and threshold parameters. The first column of Table 5 shows the tools, programs, and algorithms used, the second column provides brief descriptions thereof, the third column presents appropriate references, all of which are incorporated by reference herein in their entirety, and the fourth column presents, where applicable, the scores, probability values, and other parameters used to evaluate the strength of a match between two sequences (the higher the score, the greater the homology between two sequences). Sequences were analyzed using MACDNASIS PRO software (Hitachi Software Engineering, South San Francisco CA) and LASERGENE software (DNASTAR). Polynucleotide and polypeptide sequence alignments were generated using the default parameters specified by the clustal algorithm as incorporated into the MEGALIGN multisequence alignment program (DNASTAR), which also calculates the percent identity between aligned sequences.

The polynucleotide sequences were validated by removing vector, linker, and polyA sequences and by masking ambiguous bases, using algorithms and programs based on BLAST, dynamic programing, and dinucleotide nearest neighbor analysis. The sequences were then queried against a selection of public databases such as the GenBank primate, rodent, mammalian, vertebrate, and eukaryote databases, and BLOCKS, PRINTS, DOMO, PRODOM, and PFAM to acquire annotation using programs based on BLAST, FASTA, and BLIMPS. The sequences were assembled into full length polynucleotide sequences using programs based on Phred, Phrap, and Consed, and were screened for open reading frames using programs based on GeneMark, BLAST, and FASTA. The full length polynucleotide sequences were translated to derive the corresponding full length amino acid sequences, and these full length sequences were subsequently analyzed by querying against databases such as the GenBank databases (described above), SwissProt, BLOCKS, PRINTS, DOMO, PRODOM, Prosite, and Hidden Markov Model (HMM)-based protein family databases such as PFAM. HMM is a probabilistic approach which analyzes consensus primary structures of gene families. (See, e.g., Eddy, S.R. (1996) Curr. Opin. Struct. Biol. 6:361-365.)

The programs described above for the assembly and analysis of full length polynucleotide and amino acid sequences were also used to identify polynucleotide sequence fragments from SEQ ID

NO:56-110. Fragments from about 20 to about 4000 nucleotides which are useful in hybridization and amplification technologies were described in The Invention section above.

IV. Northern Analysis

Northern analysis is a laboratory technique used to detect the presence of a transcript of a gene and involves the hybridization of a labeled nucleotide sequence to a membrane on which RNAs from a particular cell type or tissue have been bound. (See, e.g., Sambrook, supra, ch. 7; Ausubel, 1995, supra, ch. 4 and 16.)

Analogous computer techniques applying BLAST were used to search for identical or related molecules in nucleotide databases such as GenBank or LIFESEQ (Incyte Pharmaceuticals). This analysis is much faster than multiple membrane-based hybridizations. In addition, the sensitivity of the computer search can be modified to determine whether any particular match is categorized as exact or similar. The basis of the search is the product score, which is defined as:

$$\frac{\%\text{ sequence identity} \times \%\text{ maximum BLAST score}}{100}$$

The product score takes into account both the degree of similarity between two sequences and the length of the sequence match. For example, with a product score of 40, the match will be exact within a 1% to 2% error, and, with a product score of 70, the match will be exact. Similar molecules are usually identified by selecting those which show product scores between 15 and 40, although lower scores may identify related molecules.

The results of northern analyses are reported as a percentage distribution of libraries in which the transcript encoding NuABP occurred. Analysis involved the categorization of cDNA libraries by organ/tissue and disease. The organ/tissue categories included cardiovascular, dermatologic, developmental, endocrine, gastrointestinal, hematopoietic/immune, musculoskeletal, nervous, reproductive, and urologic. The disease/condition categories included cancer, inflammation, trauma, cell proliferation, neurological, and pooled. For each category, the number of libraries expressing the sequence of interest was counted and divided by the total number of libraries across all categories. Percentage values of tissue-specific and disease- or condition-specific expression are reported in Table 3.

V. Extension of NuABP Encoding Polynucleotides

The full length nucleic acid sequences of SEQ ID NO:56-110 were produced by extension of an appropriate fragment of the full length molecule using oligonucleotide primers designed from this fragment. One primer was synthesized to initiate 5' extension of the known fragment, and the other primer, to initiate 3' extension of the known fragment. The initial primers were designed using OLIGO 4.06 software (National Biosciences), or another appropriate program, to be about 22 to 30 nucleotides in length, to have a GC content of about 50% or more, and to anneal to the target

sequence at temperatures of about 68°C to about 72°C. Any stretch of nucleotides which would result in hairpin structures and primer-primer dimerizations was avoided.

Selected human cDNA libraries were used to extend the sequence. If more than one extension was necessary or desired, additional or nested sets of primers were designed.

High fidelity amplification was obtained by PCR using methods well known in the art. PCR was performed in 96-well plates using the PTC-200 thermal cycler (MJ Research, Inc.). The reaction mix contained DNA template, 200 nmol of each primer, reaction buffer containing Mg^{2-}. $(NH_4)_2SO_4$, and β-mercaptoethanol, Taq DNA polymerase (Amersham Pharmacia Biotech), ELONGASE enzyme (Life Technologies), and Pfu DNA polymerase (Stratagene), with the following parameters for primer pair PCI A and PCI B: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C. In the alternative, the parameters for primer pair T7 and SK+ were as follows: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 57°C, 1 min; Step 4: 68°C, 2 min; Step 5: Steps 2, 3, and 4 repeated 20 times; Step 6: 68°C, 5 min; Step 7: storage at 4°C.

The concentration of DNA in each well was determined by dispensing 100 µl PICOGREEN quantitation reagent (0.25% (v/v) PICOGREEN; Molecular Probes, Eugene OR) dissolved in 1X TE and 0.5 µl of undiluted PCR product into each well of an opaque fluorimeter plate (Corning Costar, Acton MA), allowing the DNA to bind to the reagent. The plate was scanned in a Fluoroskan II (Labsystems Oy, Helsinki, Finland) to measure the fluorescence of the sample and to quantify the concentration of DNA. A 5 μl to 10 μl aliquot of the reaction mixture was analyzed by electrophoresis on a 1 % agarose mini-gel to determine which reactions were successful in extending the sequence.

The extended nucleotides were desalted and concentrated, transferred to 384-well plates, digested with CviJI cholera virus endonuclease (Molecular Biology Research, Madison WI), and sonicated or sheared prior to religation into pUC 18 vector (Amersham Pharmacia Biotech). For shotgun sequencing, the digested nucleotides were separated on low concentration (0.6 to 0.8%) agarose gels, fragments were excised, and agar digested with Agar ACE (Promega). Extended clones were religated using T4 ligase (New England Biolabs, Beverly MA) into pUC 18 vector (Amersham Pharmacia Biotech), treated with Pfu DNA polymerase (Stratagene) to fill-in restriction site overhangs, and transfected into competent E. coli cells. Transformed cells were selected on antibiotic-containing media, individual colonies were picked and cultured overnight at 37°C in 384-well plates in LB/2x carb liquid media.

The cells were lysed, and DNA was amplified by PCR using Taq DNA polymerase (Amersham Pharmacia Biotech) and Pfu DNA polymerase (Stratagene) with the following parameters: Step 1: 94°C, 3 min; Step 2: 94°C, 15 sec; Step 3: 60°C, 1 min; Step 4: 72°C, 2 min;

Step 5: steps 2, 3, and 4 repeated 29 times; Step 6: 72°C, 5 min; Step 7: storage at 4°C. DNA was quantified by PICOGREEN reagent (Molecular Probes) as described above. Samples with low DNA recoveries were reamplified using the same conditions as described above. Samples were diluted with 20% dimethysulfoxide (1:2, v/v), and sequenced using DYENAMIC energy transfer sequencing primers and the DYENAMIC DIRECT kit (Amersham Pharmacia Biotech) or the ABI PRISM BIGDYE Terminator cycle sequencing ready reaction kit (Perkin-Elmer).

In like manner, the nucleotide sequences of SEQ ID NO:56-110 are used to obtain 5' regulatory sequences using the procedure above, oligonucleotides designed for such extension, and an appropriate genomic library.

VI. Labeling and Use of Individual Hybridization Probes

Hybridization probes derived from SEQ ID NO:56-110 are employed to screen cDNAs, genomic DNAs, or mRNAs. Although the labeling of oligonucleotides, consisting of about 20 base pairs, is specifically described, essentially the same procedure is used with larger nucleotide fragments. Oligonucleotides are designed using state-of-the-art software such as OLIGO 4.06 software (National Biosciences) and labeled by combining 50 pmol of each oligomer, 250 μCi of [γ-^{32}P] adenosine triphosphate (Amersham Pharmacia Biotech), and T4 polynucleotide kinase (DuPont NEN, Boston MA). The labeled oligonucleotides are substantially purified using a SEPHADEX G-25 superfine size exclusion dextran bead column (Amersham Pharmacia Biotech). An aliquot containing 10^7 counts per minute of the labeled probe is used in a typical membrane-based hybridization analysis of human genomic DNA digested with one of the following endonucleases: Ase I, Bgl II, Eco RI, Pst I, Xba I, or Pvu II (DuPont NEN).

The DNA from each digest is fractionated on a 0.7% agarose gel and transferred to nylon membranes (Nytran Plus, Schleicher & Schuell, Durham NH). Hybridization is carried out for 16 hours at 40°C. To remove nonspecific signals, blots are sequentially washed at room temperature under conditions of up to, for example, 0.1 x saline sodium citrate and 0.5% sodium dodecyl sulfate. Hybridization patterns are visualized using autoradiography or an alternative imaging means and compared.

VII. Microarrays

A chemical coupling procedure and an ink jet device can be used to synthesize array elements on the surface of a substrate. (See, e.g., Baldeschweiler, supra.) An array analogous to a dot or slot blot may also be used to arrange and link elements to the surface of a substrate using thermal, UV, chemical, or mechanical bonding procedures. A typical array may be produced by hand or using available methods and machines and contain any appropriate number of elements. After hybridization, nonhybridized probes are removed and a scanner used to determine the levels and patterns of fluorescence. The degree of complementarity and the relative abundance of each probe

which hybridizes to an element on the microarray may be assessed through analysis of the scanned images.

Full-length cDNAs, Expressed Sequence Tags (ESTs). or fragments thereof may comprise the elements of the microarray. Fragments suitable for hybridization can be selected using software well known in the art such as LASERGENE software (DNASTAR). Full-length cDNAs, ESTs, or fragments thereof corresponding to one of the nucleotide sequences of the present invention, or selected at random from a cDNA library relevant to the present invention, are arranged on an appropriate substrate, e.g., a glass slide. The cDNA is fixed to the slide using, e.g., UV cross-linking followed by thermal and chemical treatments and subsequent drying. (See, e.g., Schena, M. et al. (1995) Science 270:467-470; Shalon, D. et al. (1996) Genome Res. 6:639-645.) Fluorescent probes are prepared and used for hybridization to the elements on the substrate. The substrate is analyzed by procedures described above.

VIII. Complementary Polynucleotides

Sequences complementary to the NuABP-encoding sequences, or any parts thereof, are used to detect, decrease, or inhibit expression of naturally occurring NuABP. Although use of oligonucleotides comprising from about 15 to 30 base pairs is described, essentially the same procedure is used with smaller or with larger sequence fragments. Appropriate oligonucleotides are designed using OLIGO 4.06 software (National Biosciences) and the coding sequence of NuABP. To inhibit transcription, a complementary oligonucleotide is designed from the most unique 5' sequence and used to prevent promoter binding to the coding sequence. To inhibit translation, a complementary oligonucleotide is designed to prevent ribosomal binding to the NuABP-encoding transcript.

IX. Expression of NuABP

Expression and purification of NuABP is achieved using bacterial or virus-based expression systems. For expression of NuABP in bacteria, cDNA is subcloned into an appropriate vector containing an antibiotic resistance gene and an inducible promoter that directs high levels of cDNA transcription. Examples of such promoters include, but are not limited to, the *trp-lac* (*tac*) hybrid promoter and the T5 or T7 bacteriophage promoter in conjunction with the *lac* operator regulatory element. Recombinant vectors are transformed into suitable bacterial hosts, e.g., BL21(DE3). Antibiotic resistant bacteria express NuABP upon induction with isopropyl beta-D-thiogalactopyranoside (IPTG). Expression of NuABP in eukaryotic cells is achieved by infecting insect or mammalian cell lines with recombinant Autographica californica nuclear polyhedrosis virus (AcMNPV), commonly known as baculovirus. The nonessential polyhedrin gene of baculovirus is replaced with cDNA encoding NuABP by either homologous recombination or bacterial-mediated transposition involving transfer plasmid intermediates. Viral infectivity is maintained and the strong polyhedrin promoter drives high levels of cDNA transcription. Recombinant baculovirus is used to

infect Spodoptera frugiperda (Sf9) insect cells in most cases, or human hepatocytes, in some cases. Infection of the latter requires additional genetic modifications to baculovirus. (See Engelhard, E.K. et al. (1994) Proc. Natl. Acad. Sci. USA 91:3224-3227; Sandig, V. et al. (1996) Hum. Gene Ther. 7:1937-1945.)

In most expression systems, NuABP is synthesized as a fusion protein with, e.g., glutathione S-transferase (GST) or a peptide epitope tag, such as FLAG or 6-His, permitting rapid, single-step, affinity-based purification of recombinant fusion protein from crude cell lysates. GST, a 26-kilodalton enzyme from Schistosoma japonicum, enables the purification of fusion proteins on immobilized glutathione under conditions that maintain protein activity and antigenicity (Amersham Pharmacia Biotech). Following purification, the GST moiety can be proteolytically cleaved from NuABP at specifically engineered sites. FLAG, an 8-amino acid peptide, enables immunoaffinity purification using commercially available monoclonal and polyclonal anti-FLAG antibodies (Eastman Kodak). 6-His, a stretch of six consecutive histidine residues, enables purification on metal-chelate resins (QIAGEN). Methods for protein expression and purification are discussed in Ausubel (1995, supra, ch. 10 and 16). Purified NuABP obtained by these methods can be used directly in the following activity assay.

X. Demonstration of NuABP Activity

NuABP activity is measured by its ability to stimulate transcription of a reporter gene (Liu, H.Y. et al. (1997) EMBO J. 16(17):5289-5298.) The assay entails the use of a well characterized reporter gene construct, $LexA_{op}$-LacZ, that consists of LexA DNA transcriptional control elements ($LexA_{op}$) fused to sequences encoding the E. coli LacZ enzyme. The methods for constructing and expressing fusions genes, introducing them into cells, and measuring LacZ enzyme activity, are well known to those skilled in the art. Sequences encoding NuABP are cloned into a plasmid that directs the synthesis of a fusion protein, LexA-NuABP, consisting of NuABP and a DNA binding domain derived from the LexA transcription factor. The resulting plasmid, encoding a LexA-NuABP fusion protein, is introduced into yeast cells along with a plasmid containing the $LexA_{op}$-LacZ reporter gene. The amount of LacZ enzyme activity associated with LexA-NuABP transfected cells, relative to control cells, is proportional to the amount of transcription stimulated by the NuABP.

XI. Functional Assays

NuABP function is assessed by expressing the sequences encoding NuABP at physiologically elevated levels in mammalian cell culture systems. cDNA is subcloned into a mammalian expression vector containing a strong promoter that drives high levels of cDNA expression. Vectors of choice include pCMV SPORT (Life Technologies) and pCR3.1 (Invitrogen, Carlsbad CA), both of which contain the cytomegalovirus promoter. 5-10 μg of recombinant vector are transiently transfected into a human cell line, for example, an endothelial or hematopoietic cell

line, using either liposome formulations or electroporation. 1-2 μg of an additional plasmid containing sequences encoding a marker protein are co-transfected. Expression of a marker protein provides a means to distinguish transfected cells from nontransfected cells and is a reliable predictor of cDNA expression from the recombinant vector. Marker proteins of choice include, e.g., Green Fluorescent Protein (GFP; Clontech), CD64, or a CD64-GFP fusion protein. Flow cytometry (FCM), an automated, laser optics-based technique, is used to identify transfected cells expressing GFP or CD64-GFP and to evaluate the apoptotic state of the cells and other cellular properties. FCM detects and quantifies the uptake of fluorescent molecules that diagnose events preceding or coincident with cell death. These events include changes in nuclear DNA content as measured by staining of DNA with propidium iodide; changes in cell size and granularity as measured by forward light scatter and 90 degree side light scatter; down-regulation of DNA synthesis as measured by decrease in bromodeoxyuridine uptake; alterations in expression of cell surface and intracellular proteins as measured by reactivity with specific antibodies; and alterations in plasma membrane composition as measured by the binding of fluorescein-conjugated Annexin V protein to the cell surface. Methods in flow cytometry are discussed in Ormerod, M.G. (1994) Flow Cytometry, Oxford, New York NY.

The influence of NuABP on gene expression can be assessed using highly purified populations of cells transfected with sequences encoding NuABP and either CD64 or CD64-GFP. CD64 and CD64-GFP are expressed on the surface of transfected cells and bind to conserved regions of human immunoglobulin G (IgG). Transfected cells are efficiently separated from nontransfected cells using magnetic beads coated with either human IgG or antibody against CD64 (DYNAL, Lake Success NY). mRNA can be purified from the cells using methods well known by those of skill in the art. Expression of mRNA encoding NuABP and other genes of interest can be analyzed by northern analysis or microarray techniques.

XII. Production of NuABP Specific Antibodies

NuABP substantially purified using polyacrylamide gel electrophoresis (PAGE; see, e.g., Harrington, M.G. (1990) Methods Enzymol. 182:488-495), or other purification techniques, is used to immunize rabbits and to produce antibodies using standard protocols.

Alternatively, the NuABP amino acid sequence is analyzed using LASERGENE software (DNASTAR) to determine regions of high immunogenicity, and a corresponding oligopeptide is synthesized and used to raise antibodies by means known to those of skill in the art. Methods for selection of appropriate epitopes, such as those near the C-terminus or in hydrophilic regions are well described in the art. (See, e.g., Ausubel, 1995, supra, ch. 11.)

Typically, oligopeptides of about 15 residues in length are synthesized using an ABI 431A peptide synthesizer (Perkin-Elmer) using fmoc-chemistry and coupled to KLH (Sigma-Aldrich, St. Louis MO) by reaction with N-maleimidobenzoyl-N-hydroxysuccinimide ester (MBS) to increase

immunogenicity. (See. e.g., Ausubel, 1995, supra.) Rabbits are immunized with the oligopeptide-KLH complex in complete Freund's adjuvant. Resulting antisera are tested for antipeptide and anti-NuABP activity by, for example, binding the peptide or NuABP to a substrate, blocking with 1% BSA, reacting with rabbit antisera, washing, and reacting with radio-iodinated goat anti-rabbit IgG.

XIII. Purification of Naturally Occurring NuABP Using Specific Antibodies

Naturally occurring or recombinant NuABP is substantially purified by immunoaffinity chromatography using antibodies specific for NuABP. An immunoaffinity column is constructed by covalently coupling anti-NuABP antibody to an activated chromatographic resin, such as CNBr-activated SEPHAROSE (Amersham Pharmacia Biotech). After the coupling, the resin is blocked and washed according to the manufacturer's instructions.

Media containing NuABP are passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of NuABP (e.g., high ionic strength buffers in the presence of detergent). The column is eluted under conditions that disrupt antibody/NuABP binding (e.g., a buffer of pH 2 to pH 3, or a high concentration of a chaotrope, such as urea or thiocyanate ion), and NuABP is collected.

XIV. Identification of Molecules Which Interact with NuABP

NuABP, or biologically active fragments thereof, are labeled with ^{125}I Bolton-Hunter reagent. (See, e.g., Bolton A.E. and W.M. Hunter (1973) Biochem. J. 133:529-539.) Candidate molecules previously arrayed in the wells of a multi-well plate are incubated with the labeled NuABP, washed, and any wells with labeled NuABP complex are assayed. Data obtained using different concentrations of NuABP are used to calculate values for the number, affinity, and association of NuABP with the candidate molecules.

Various modifications and variations of the described methods and systems of the invention will be apparent to those skilled in the art without departing from the scope and spirit of the invention. Although the invention has been described in connection with certain embodiments, it should be understood that the invention as claimed should not be unduly limited to such specific embodiments. Indeed, various modifications of the described modes for carrying out the invention which are obvious to those skilled in molecular biology or related fields are intended to be within the scope of the following claims.

TABLE 1

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
1	56	025733	SPLNFET01	025733H1 and 025733X307D2 (SPLNFET01), 1519809F1 and 1519809T1 (BLADTUT04), 1526288T6 (UCMCL5T01), 1595557X16C1 and 1595557X19C1 (BRAINOT14), 1903359F6 (OVARNOT07), 2417225F6 (HNT3AZT01), 4283542H1 (LIVRDIR01)
2	57	079702	SYNORAB01	002190H1 (U937NOT01), 079479F1 and 079702H1 (SYNORAB01), 125223T6 (LUNGNOT01), 371006R6 (LUNGNOT02), 2129460T6 (KIDNNOT05), 2999366H1 (TLYMNOT06), 3031905F6 (TLYMNOT05), 4949863H1 (SINTNOT25)
3	58	116208	KIDNNOT01	116208H1 and 116208R1 (KIDNNOT01), 2293058R6 (BRAINON01), 3731418H1 and 3731418T6 (SMCCNON03)
4	59	179261	PLACNOB01	179261H1 (PLACNOB01), 3666231F6 and 3666231T6 (PANCNOT16)
5	60	259161	HNT2RAT01	259161H1 (HNT2RAT01), 1005021R6 (BRSTNOT03), 2634660H1 (COLNTUT15), 2894335H1 (KIDNTUT14), 2924845H1 (SININOT04), 3659440H1 (ENDPNOT02), SBMA02955F1, SBMA03577F1, SBMA01445F1, SBMA00985F1, SBMA01499F1
6	61	320087	EOSIHET02	016657F1 (HUVELPB01), 320087H1 (EOSIHET02), 824110R1 (PROSNOT06), 987467H1 (LVENNOT03), 1235752F1 (LUNGFET03), 1361280F1 (LUNGNOT12), 1389740H1 (EOSINOT01), 1534332F1 (SPLNNOT04), 1813754F6 (SKINBIT01), 4184915H1 (BRSTNOT31), 5306522H1 (MONOTXT02)
7	62	491271	HNT2AGT01	363816X3 and 363816X9 (PROSNOT01), 491271F1, 491271H1 and 491271T6 (HNT2AGT01), 967354R6, 967354X15 and 967354X27 (BRSTNOT05), 2733444H1 (OVARTUT04)
8	63	585172	PROSNOT02	395188R6 (TMLR2DT01), 585172H1 (PROSNOT02), 864269T1 (BRAITUT03), 1417965F1 (KIDNNOT09)
9	64	615200	COLNTUT02	615200H1 and 615200R6 (COLNTUT02), 1213980R1 (BRSTTUT01), SBPA02731D1, SBPA00184D1
10	65	997067	KIDNTUT01	125981X3 (LUNGNOT01), 997067H1, 997067R6 and 997067T6 (KIDNTUT01), 1448201H1 (PLACNOT02), 1663447H1 (BRSTNOT09), 1889314H1 (BLADTUT07), 1918706H1 (PROSNOT06), 2699956H1 (OVARTUT10), 2702585H1 (OVARTUT10), 2900479H1 (DRGCNOT01), 3595727T6 (FIBPNOT01), 4309131H1 (BRAUNOT01)
11	66	1443262	THYRNOT03	1257005F1 (MENITUT03), 1443262H1 (THYRNOT03), 1618906F6 (BRAITUT12), 2474133T6 (THP1NOT03), 3594075H1 (FIBPNOT01), 4914442H1 (LIVRFET05)

TABLE 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
12	67	1521648	BLADTUT04	292172H1 (TMLR3DT01), 819925R6 (KERANOT02), 1353913H1 (LATRTUT02), 1521648H1 and 1522364F1 (BLADTUT04), 1963178H1 (BRSTNOT04), 2342505F6 (TESTTUT02), 4899970H1 (OVARDIT01), 5043585H2 (PLACFER01)
13	68	1685494	PROSNOT15	903980X13, 903980X14 and 903980X17 (COLNNOT07), 1685494H1 (PROSNOT15), 4164127T6 (BRSTNOT32)
14	69	1730829	BRSTTUT08	116146R1 (KIDNNOT01), 836856R1 (PROSNOT07), 1730829H1, 1730829X11C1, 1730829X12C1 and 1730829X13C1 (BRSTTUT08), 1959889R6 (BRSTNOT04), 2188079H1 (PROSNOT26), 3384625H1 (ESOGNOT04)
15	70	1864641	PROSNOT19	1844972H1 (COLNNOT08), 1864641F6 and 1864641H1 (PROSNOT19), 3090702T6 (BRSTNOT19), 3411665H1 (BRSTTUS08), 5152366H1 (HEARFET03), 5166179H1 (MUSCDMT01)
16	71	2444604	THP1NOT03	1506658F1 (BRAITUT07), 1532034F1 (SPLNNOT04), 2444604H1 (THP1NOT03)
17	72	2445008	THP1NOT03	605598X12 (BRSTTUT01), 628644H1 (KIDNNOT05), 732124R1 (LUNGNOT03), 819194R1 (KERANOT02), 1259467H1 (MENITUT03), 1363205F6 (LUNGNOT12), 1901312T6 (BLADTUT06), 2445008H1 (THP1NOT03), 2681125H1 (SINIUCT01)
18	73	2572462	HIPOAZT01	396323R6 (PITUNOT02), 863622H1 (BRAITUT03), 1848956F6 and 1848956T6 (LUNGFET03), 2345947H1 (TESTTUT02), 2396384F6 (THP1AZT01), 2572462H1 (HIPOAZT01), 2650980F6 (LUNGTUT12), 2814325H1 (OVARNOT10), 5076051H1 (COLCTUT03)
19	74	2572892	HIPOAZT01	030596X15R1 (THP1NOB01), 539564X11 (LNODNOT02), 1275514F1 and 1275514T6 (TESTTUT02), 2112383H1 (BRAITUT03), 2572892H1 (HIPOAZT01), 2986518H1 (CARGDIT01)
20	75	2785674	BRSTNOT13	261399H1 (HNT2AGT01), 1274739F1 (TESTTUT02), 2785674H1 (BRSTNOT13)
21	76	2797479	NPOLNOT01	302614X13 (TESTNOT04), 2797479H1 (NPOLNOT01), SAIA02597F1, SAIA00739F1, SAIA02537F1
22	77	2960640	ADRENOT09	027211R1, 027211X1 and 027211X3 (SPLNFET01), 1401538F6 (BRAITUT08), 2496984F6 (ADRETUT05), 2960640H1 (ADRENOT09), 3211036T6 (BLADNOT08)
23	78	3454051	SPLNNOT11	279331R6 (LIVRNOT02), 2515972T6 and 2516010T6 (LIVRTUT04), 2910726F6 (KIDNTUT15), 3454051H1 (SPLNNOT11)

TABLE 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
24	79	3510640	CONCNOT01	556354H1 (MPHGLPT02), 581085H1 (BRAVTXT05), 990636R6 (COLNNOT11), 1799185F6 and 1799185T6 (COLNNOT27), 3510640H1 (CONCNOT01), 4326648H1 (TLYMUNT01), SBHA01099F1
25	80	3815083	TONSNOT03	2026951R6 and 2026951T6 (KERANOT02), 2300211R6 (BRSTNOT05), 2505283F6 (CONUTUT01), 3187267R6 (THYMNON04), 3815083H1 and 3815083T6 (TONSNOT03)
26	81	3988457	LUNGNON03	609622R6 (COLNNOT01), 1710465F6 (PROSNOT16), 3988457H1 (LUNGNON03), SAQA00089F1, SAQA03055F1, SAQB00279F1
27	82	131890	BMARNOT02	131890H1 (BMARNOT02), 131890T6 (BMARNOT02), 132849R6 (BMARNOT02), 3357071F6 (PROSTUT16)
28	83	238642	SINTNOT02	238642H1 (SINTNOT02), 1620593F6 (BRAITUT13), 1620593H1 (BRAITUT13), 1620593T6 (BRAITUT13), 2534087F6 (BRAINOT18)
29	84	669862	CRBLNOT01	347231X7 (THYMNOT02), 669862H1 (CRBLNOT01), 2244458R6 (HIPONON02), 2244458T6 (HIPONON02), 2622610T6 (KERANOT02), 3536262H1 (KIDNNOT25), 4204212H1 (BRAITUT29)
30	85	1003663	BRSTNOT03	850478T1 (NGANNOT01), 1003663H1 (BRSTNOT03), 1252179F2 (LUNGFET03), 1293336F1 (PGANNOT03), 1813002F6 (PROSTUT12), 2101974R6 (BRAITUT02)
31	86	1432557	BEPINON01	1314545F6 (BLADTUT02), 1432557H1 (BEPINON01), 1443311R1 (THYRNOT03), 1705738F6 (DUODNOT02), 2182184F6 (SININOT01)
32	87	1441770	THYRNOT03	035105R1 (HUVENOB01), 1441770H1 (THYRNOT03), 1500943F1 (SINTBST01), 2542840H1 (UTRSNOT11), 4533672H1 (OVARNOT12)
33	88	1456684	COLNFET02	1456684F6 (COLNFET02), 1456684H1 (COLNFET02), 1456684T6 (COLNFET02), 1992143H1 (CORPNOT02), 2687476F6 (LUNGNOT23), 3139175F6 (SMCCNOT02), 4746319H1 (SMCRUNT01)
34	89	1602916	BLADNOT03	3397976X305D2 (UTRSNOT16)
35	90	1692816	COLNNOT23	999017R6 (KIDNTUT01), 1342490T1 (COLNTUT03), 1421981F1 (KIDNNOT09), 1692816H1 (COLNNOT23), 2176832F6 (ENDCNOT03), 2451404F6 (ENDANOT01)
36	91	1968191	BRSTNOT04	1968191H1 (BRSTNOT04), 1968191T6 (BRSTNOT04), 2752967R6 (THP1AZS08), 3281163T6 (STOMFET02), 3748607H1 (UTRSNOT18)
37	92	2052061	LIVRFET02	003803X8 (HMC1NOT01), 027044X1 (SPLNFET01), 027044X101 (SPLNFET01), 2052061H1 (LIVRFET02), 3931936F6 (PROSTUT09)

TABLE 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
38	93	2056207	BEPINOT01	071525F1 (PLACNOB01), 162720R1 (ADENINB01), 270498H1 (HNT2NOT01), 1477853T1 (CORPNOT02), 1931058F6 (COLNTUT03), 2056207H1 (BEPINOT01), 2056207X11R1 (BEPINOT01), 2231060F6 (PROSNOT16), 2420063X309D4 (SCORNON02), 3424630H1 (BRSTNOR01), 3873760F6 (HEARNOT06), 3873760T6 (HEARNOT06), SBOA00627D1, SCJA02192V1, SCJA02089V1
39	94	2101803	BRAITUT02	399584R6 (PITUNOT02), 399584T6 (PITUNOT02), 1649058F6 (PROSTUT09), 1902809F6 (OVARNOT07), 2101803H1 (BRAITUT02), 2101803R6 (BRAITUT02), 3098623H1 (CERVNOT03)
40	95	2112362	BRAITUT03	948628R1 (PANCNOT05), 1209447T1 (BRSTNOT02), 1814624F6 (PROSNOT20), 2112362H1 (BRAITUT03), 2945621H1 (BRAITUT23), 3285663H1 (HEAONOT05), 3526403H1 (ESOGTUN01), 5032729H1 (ENDIUNT01), 5099417H1 (PROSTUS20)
41	96	2117346	BRSTTUT02	487994R6 (HNT2AGT01), 952855R1 (SCORNON01), 952855T1 (SCORNON01), 2117346H1 (BRSTTUT02), 2458342F6 (ENDANOT01), 2731585H1 (OVARTUT04), 3475780H1 (LUNGNOT27), 3538525F6 (SEMVNOT04)
42	97	2119917	BRSTTUT02	2119917H1 (BRSTTUT02), 2791421F6 (COLNTUT16), 2794083F6 (COLNTUT16), 5006921H1 (STOMNOT08)
43	98	2123456	BRSTNOT07	484031H1 (HNT2RAT01), 617559F1 (PGANNOT01), 617559R1 (PGANNOT01), 1575977F1 (LNODNOT03), 2123456H1 (BRSTNOT07), 2958712H1 (ADRENOT09), 3764961H1 (BRSTNOT24)
44	99	2148792	BRAINOT09	1732781F6 (BRSTTUT08), 2050885F6 (LIVRFET02), 2148792H1 (BRAINOT09), 2590822H1 (LUNGNOT22), 2972368T6 (HEAONOT02), SBQA00396D1, SBQA03678D1, SBQA02120D1, SBQA03269D1
45	100	2751943	THP1AZS08	1720187X16C1 (BLADNOT06), 2751943H1 (THP1AZS08), 3492378H1 (ADRETUT07)
46	101	3128913	LUNGTUT12	2551859F6 (LUNGTUT06), 3128913H1 (LUNGTUT12), SBMA01861F1, SBMA02298F1, SBMA01013F1, SBMA02403F1, SBMA01362F1
47	102	3282941	HEAONOT05	154741R6 (THP1PLB02), 155904R6 (THP1PLB02), 157816R1 (THP1PLB02), 979920H1 (TONGTUT01), 1233933T6 (LUNGFET03), 1657077F6 (URETTUT01), 2445017F6 (THP1NOT03), 3282941H1 (HEAONOT05), 3341633H1 (SPLNNOT09), 3517140H1 (LUNGNON03)
48	103	3286656	HEAONOT05	898123H1 (BRSTNOT05), 3286656H1 (HEAONOT05), 3641429T6 (LUNGNOT30), 3657668F6 (ENDPNOT02)

TABLE 1 (cont.)

Protein SEQ ID NO:	Nucleotide SEQ ID NO:	Clone ID	Library	Fragments
49	104	3490802	EPIGNOT01	2238441H1 (PANCTUT02), 2700133F6 (OVARTUT10), 2700133T6 (OVARTUT10), 3490226H1 (EPIGNOT01), 3490802H1 (EPIGNOT01), 4822929H1 (PROSTUT17)
50	105	3507366	CONCNOT01	2130284H1 (KIDNNOT05), 3507366H1 (CONCNOT01), 3557087F6 (LUNGNOT31), 4241774H1 (SYNWDIT01)
51	105	3573060	BRONNOT01	3573060F6 (BRONNOT01), 3573060H1 (BRONNOT01), 3573060T6 (BRONNOT01), 3867263H1 (BRAITUT07), 5013346H1 (BRAXNOT03)
52	107	3573661	BRONNOT01	3028034F6 (HEARFET02), 3152642H1 (ADRENON04), 3573661F6 (BRONNOT01), 3573661H1 (BRONNOT01), 3577568F6 (BRONNOT01)
53	108	3633422	LIVRNOT03	033412R6 (THP1NOB01), 074123F1 (THP1PEB01), 263241H1 (HNT2AGT01), 748567R1 (BRAITUT01), 1292088T1 (PGANNOT03), 1517449T1 (PANCTUT01), 3633422H1 (LIVRNOT03)
54	109	3993377	LUNGNON03	3003233H1 (TLYMNOT06), 3993377H1 (LUNGNON03), 3993377T6 (LUNGNON03), 4251662F6 (BRADDIR01), SBSA02001V1
55	110	4717936	BRAIHCT02	4717936F6 (BRAIHCT02), 4717936H1 (BRAIHCT02), 4717936T6 (BRAIHCT02)

TABLE 2

Polypeptide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
1	754	S6 T15 S22 S26 S28 S30 S60 Y84 S98 S102 S103 S112 S121 S146 T166 T183 T184 S231 Y253 S303 T304 S308 T327 T361 T393 T394 T399 T448 S496 Y583 S586 T608 S635 S672 S673 S682 S691 S711 S713 S751		L435 - P474 PFAM	DNA polymerase	PFAM, BLOCKS, MOTIFS
2	593	S32 Y62 T65 S83 S141 T159 T160 S185 S254 S288 T311 S314 S333 T368 S380 S401 T410 S426 S452 S461 S479 T483 T485 T576		E102 - A157 Q201 - C252	PHD finger DNA binding protein (GI 3342452)	BLAST, PFAM, MOTIFS
3	534	T39 S52 S301 T344 S373 T404 S425 S438 S439 S440 S473 T480 S490 T527		I17 - D57 PFAM	DNA polymerase	PFAM, BLOCKS, MOTIFS
4	255	S10 S26 Y35 Y113 S149 T168 Y169 T248		Y58 - C86 F141 - H163 Y169 - H191 Y197 - H219 Y225 - H247 PFAM	C2H2-type zinc finger protein (GI 498721)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS

TABLE 2 (cont.)

Polypeptide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
5	562	T29 T43 S76 S142 S165 S202 T214 Y302 S305 Y349 S385 S500 T526 S527		Y235 - D312 PFAM	DNA helicase (GI 531243; SEQ ID NO:113)	BLAST, PFAM, BLOCKS, MOTIFS
6	432	S33 S58 T166 T172 S197 T230 T261 S275 S286 S290 S298 S338 T362 S376 T407 T409 T419		E329 - A355 BLOCKS	CCAAT-box-binding transcription factor	BLOCKS, MOTIFS
7	799	T24 S33 T43 S73 T88 S91 S110 S147 T219 S262 S323 Y380 S532 S586 S756 T795		H250 - H291 Y324 - H346 Y253 - H374 Y380 - H402 PFAM	C2H2-type zinc finger protein (GI 498727)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
8	137	S3 T38 S74 S75 S118		R85 - L97 PFAM	BTB domain/C2H2-type zinc finger protein	PFAM, PRINTS, MOTIFS
9	230	T178 S187			sirtuin type 3 (GI 5225322)	BLAST, MOTIFS
10	446	T3 S28 S32 T52 T94 T96 S135 S143 T159 T165 S171 S433		H200 - H222 Y228 - H250 Y256 - H278 Y284 - H306	zinc finger protein ZFP113 (GI 5640017)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
11	428	S72 S92 S101 S118 S120 S125 T245 T277 S289 S315 S317 Y326 S409			Skeletal muscle BOP2 (GI 5870834; SEQ ID NO:117)	BLAST, MOTIFS

TABLE 2 (cont.)

Polypeptide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
12	590	S45 Y52 T60 S83 S90 T95 T116 T145 T233 T330 S391 S410 S411 T420 T439 T490 S521			Methyl-CpG binding protein (GI 2239126)	BLAST, MOTIFS
13	479	S15 Y29 S30 S118 T173 T183 S203 S217 Y232 S235 T255 S352 S362 Y451		Y232 - H254 H283 - H305 Y311 - H333 Y339 - H361 PFAM	SRE-ZBP (GI g36603)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
14	433	S92 S96 T250 S319 T322 T327 S335 T344		C380 - C421 PFAM	C3HC4-type zinc finger protein	PFAM, BLOCKS, MOTIFS
15	320	T6 S27 T125 T172 S229 S232 T239 S248 S259 S266 Y267 S291			Zinc finger factor (GI 3150148)	BLAST, MOTIFS
16	179	S11 T21 S46 S140			Single-stranded DNA binding protein (csdp) (GI 1562534)	BLAST, MOTIFS
17	494	T73 Y80 S104 Y116 T192 S289 S297 T329 T364 T376 S387		C13 - H41 BLOCKS	Zinc finger transcription factor (GI 2895870)	BLAST, BLOCKS, MOTIFS
18	401	S4 S82 S97 T166 S188 S249 S279 S289 S290 S294 S319 S368 S371 S372 S378 T392 S396		P5 - K81 A114 - S179 G186 - P262 PFAM	HP1-BP74 (GI 1480112)	PFAM, BLOCKS, PRINTS, MOTIFS

TABLE 2 (cont.)

Polypeptide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
19	264	S11 S25 S76 S82 S90 S92 S96 S119 T229		F154 - H176 C180 - H202 F208 - H230 Y236 - C259 PFAM	C2H2-type zinc finger protein (GI 429188)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
20	153	T23 S40 T44 S110 S120 T124		R42 - E141 PFAM	High mobility group-like nuclear protein (GI 2822179)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
21	243	S20 S21 S76 S100 S104 S160 T194 S196 S212 T222 Y229		Y90 - H112 H118 - H140 Y146 - H168 Y174 - H195 PFAM	C2H2-type zinc finger protein (GI 38015)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
22	485	T29 S34 S104 S147 T162 T248 S249 S256 S347 S452 S477		S309 - H331 H337 - H359 Y365 - H387 Y393 - H415 PFAM	BTB domain/C2H2-type zinc finger protein (GI 2843171)	BLAST, PFAM, BLOCKS, PRINTS, MOTIFS
23	160	S118		C5 - F62 C80 - F137 PFAM	LIM domain protein/CRP2 (GI 487284)	BLAST, PFAM, BLOCKS, PROFILESCAN, MOTIFS
24	511	S10 T36 S75 S90 S222 T245 T259 S399 S405 Y443 S500		Y171 - P223 Y267 - K294 BLOCKS	2'-5'oligoadenylate synthetase-related protein p56 (GI 4731857)	BLOCKS, MOTIFS
25	310	S24 S39 T69 Y104 S185 T282 T296			SIR2 family transcriptional regulatory protein (GI 2648874)	BLAST, MOTIFS

TABLE 2 (cont.)

Polypeptide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
26	331	T29 S40 S74 S257 T270 S301		V112 - R134 BLOCKS	Histone protein	BLOCKS, MOTIFS
27	200	T43 S123 T129 S167 S183 S184			Zinc finger protein (g1373394)	MOTIFS BLAST
28	100	S44 Y25 Y98		Transcription anti-terminator; bglG family: E47-I100	transcription elongation factor (g4336506)	MOTIFS BLAST BLOCKS
29	528	S204 T487 S29 S34 T48 T227 S327 T367 T423 S483 Y39 Y44 Y112 Y163	N24 N52 N100 N481	C2H2 zinc fingers: Y191-H213 Y247-H269 Y275-H297 Y331-H353 Y387-H409 Y415-H437 Y443-H465 Y471-H493	Zinc finger protein (g498721)	MOTIFS BLAST BLOCKS PFAM
30	350	T264 S305	N33 N79	C3HC4 RING finger: C230-C271	C3HC4/RING zinc finger protein (g1321818)	MOTIFS BLAST BLOCKS PFAM PROFILESCAN
31	315	S51 T94 S121 S123 S142 S143 T184 S232 S252 T36 T46 S159 S163 S168			Similar to CCAAT/enhancer-binding protein (g1947129)	MOTIFS BLAST
32	120	S36 S56 T93 S104	N98 N103	bZIP transcription factor: P21-P85		MOTIFS PFAM BLOCKS

TABLE 2 (cont.)

Polypeptide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
33	326	S59 S38 T207 S284 T319 T43 S80 T137 T155 T211 S238 T239	N209	C2H2 zinc fingers: C143-C171 Y169-H191 F197-H219	Zinc finger protein (g220643)	MOTIFS BLAST PFAM BLOCKS
34	106	S80 T89 T39 T53		Homeobox: R14-K70	CHOX M product; homeobox protein (g62701)	MOTIFS BLAST BLOCKS PFAM PROFILESCAN
35	209	S176 T180 S184 T193 S201 S4 T25 S49	N18	bZIP transcription factor: K115-E140	geminin (g3219357)	MOTIFS BLAST PFAM
36	212	S79 S107 T127 T202 S45 S56 S124 T152 Y35	N92	HMG box: M1-Q36	Smarcel-related protein (GI 4321968)	MOTIFS BLAST PFAM
37	359	T329 T50 S125 S224 S230 S235 S344 S31 S215 S312 Y42	N45 N340	C2H2 zinc fingers: F278-C306 Y304-H328 F334-H356	BKLF; CACCC-box binding protein (g1244515)	MOTIFS BLAST BLOCKS PFAM
38	445	S68 T87 S153 S339 S405 S55 T105 S315 S422 Y419	N337 N374 N388	C3HC4 RING fingers: C74-P120 N228-C235	ARI (RING finger) protein (g2058299)	MOTIFS BLAST BLOCKS PFAM
39	433	S283 T44 T57 T123 S136 T185 T220 S239 T268 S313 S330 T105 T109 S125 T216	N169 N206		skm-BOP2 zinc finger protein (g1809327)	MOTIFS BLAST

TABLE 2 (cont.)

Polypeptide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
40	355	T72 T84 T184 S191 T244 S88 T162 T229 T294 S330	N308 N324		Sir2 family protein (g5353746)	MOTIFS BLAST
41	443	T76 T106 S148 T309 S12 T253 S299 S357 T373 T427 Y61 Y114	N366 N425	Myb-like DNA binding domain: D72-F118	ADA2 transcriptional adaptor protein (g170991)	MOTIFS BLAST BLOCKS PFAM PROFILESCAN
42	164	S37 T55 T64 S83 S22 Y146	N117	mutT domain: V29-L70		MOTIFS BLOCKS PFAM
43	215	S79 S127 T12 T45		HMG box: M1-Q36	Sry-related protein (g211510)	MOTIFS BLAST PFAM
44	539	T15 S24 S66 S83 T97 T105 T109 S128 T149 S153 S198 T203 T225 T238 T296 S466 Y258	N465	C2H2 zinc fingers: H230-H252 Y258-H280 Y286-H308 Y314-H336 Y342-H364 F370-H392 Y398-H420 Y426-H448 Y482-H504 Y510-H532	C2H2 zinc finger protein (g5757625)	MOTIFS BLAST PFAM BLOCKS
45	182	T59 S112 S120 S100 S139 Y64			Transcriptional regulator (g2621798)	MOTIFS BLAST

TABLE 2 (cont.)

Polypeptide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
46	534	S494 S31 S44 S117 T123 S185 S216 S476 S504 S176 S182 S211 T249 S293 S323 S409 T489 Y76 Y285	N29 N39 N250 N351	C2H2 zinc fingers: Y285-H307 Y313-H335 Y341-H363 C369-H391 Y397-H419 Y425-H447 Y453-H475 Y481-H503 Y509-H531	Zinc finger protein (g1373394)	MOTIFS BLAST PFAM BLOCKS
47	206	S5 S7 S40 S45 S46 S100 S144 S26 S107 T148 S185 Y38	N44 N177	Myc-type HLH domain: Q108-R160	Musculin (g3599519)	MOTIFS BLAST PFAM BLOCKS PROFILESCAN
48	172	T5 S87 S96 S115 T124 S22 T64			KRAB zinc finger protein (g1049295)	MOTIFS BLAST
49	275	S185 S14 S48 T54 S118 T139 T161 T189 T217 Y256	N210 N214 N238 N260	C2H2 zinc fingers: F172-H194 Y200-H222 Y228-H250	Repressor transcriptional factor (g1017722)	MOTIFS BLAST PFAM BLOCKS
50	236	S157 S42 T167 T222 T81 Y213	N40	C3HC4 RING finger: P126-L150	Ariadne-2 RING finger protein (g3445441)	MOTIFS BLAST BLOCKS
51	214	S7 S8 S116 T127 S154 S191 T31 S41 T204	N2	Chromodomain: V113-E134	Nucleoplasmin (g833629)	MOTIFS BLAST BLOCKS

TABLE 2 (cont.)

Polypeptide Seq ID NO:	Amino Acid Residues	Potential Phosphorylation Sites	Potential Glycosylation Sites	Signature Sequence(s)	Identification/ Homologous Sequence	Analytical Methods and Databases
52	396	T348 T392 S118 T193 T201 S270 S294 S80 S112 S206 S260 T313 T355 S375 S387	N2	C3HC4 RING finger: C26-C50	Midline 1/ cerebellar isoform 1 RING finger protein (g3462503)	MOTIFS BLAST PFAM BLOCKS PROFILESCAN
53	486	S29 T58 S155 S239 T292 T379 S146 T271 S425			5'-nucleotidase (g633071)	MOTIFS BLAST
54	555	S432 T502 S68 S195 T199 T226 S315 T379 T441 T534 S170 S248 S282 S291 T327 T336 S391 S422 T481 Y257 Y274	N25 N66 N246 N364	ATP/GTP binding site (P-loop): A434-T441	Transcription termination factor I (TTF-I) interacting peptide 5 isoform (g2183083)	MOTIFS BLAST
55	61	T34 T42 Y48			Putative leucine-rich DNA-binding protein (g55991)	MOTIFS BLAST

TABLE 3

Nucleotide Seq ID NO:	Selected Fragment	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
56	169-215	Reproductive (0.224) Nervous (0.198) Cardiovascular (0.112)	Cell Proliferative (0.725) Inflammation (0.190)	PBLUESCRIPT
57	551-595	Hematopoietic/Immune (0.240) Reproductive (0.180) Gastrointestinal (0.120)	Cell Proliferative (0.700) Inflammation (0.360)	PBLUESCRIPT
58	541-585	Nervous (0.286) Reproductive (0.286) Cardiovascular (0.214)	Cell Proliferative (0.643) Trauma (0.214)	PBLUESCRIPT
59	109-153	Reproductive (1.000)	Cell Proliferative (1.000) Inflammation (1.000)	PBLUESCRIPT
60	435-479	Hematopoietic/Immune (0.211) Gastrointestinal (0.183) Reproductive (0.183)	Cell Proliferative (0.620) Inflammation (0.338)	PBLUESCRIPT
61	1195-1239	Reproductive (0.248) Cardiovascular (0.174) Nervous (0.157)	Cell Proliferative (0.637) Inflammation (0.256)	PBLUESCRIPT
62	217-261	Reproductive (0.429) Nervous (0.238) Cardiovascular (0.095)	Cell Proliferative (0.667) Inflammation (0.143) Trauma (0.095)	PBLUESCRIPT
63	919-963	Reproductive (0.265) Nervous (0.235) Cardiovascular (0.088)	Cell Proliferative (0.618) Inflammation (0.206)	PSPORT1
64	823-876	Reproductive (0.382) Nervous (0.176) Gastrointestinal (0.118)	Cell Proliferative (0.794)	PSPORT1
65	380-424	Reproductive (0.346) Nervous (0.154) Gastrointestinal (0.135)	Cell Proliferative (0.750) Inflammation (0.231)	PSPORT1

TABLE 3 (cont.)

Nucleotide Seq ID NO:	Selected Fragment	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
66	757-801	Nervous (0.222) Hematopoietic/Immune (0.167) Reproductive (0.167)	Cell Proliferative (0.778) Inflammation (0.222)	pINCY
67	812-856	Reproductive (0.246) Nervous (0.180) Gastrointestinal (0.148)	Cell Proliferative (0.639) Inflammation (0.246)	pINCY
68	326-370	Reproductive (0.500) Nervous (0.200) Gastrointestinal (0.150)	Cell Proliferative (0.700) Trauma (0.150)	pINCY
69	703-747	Reproductive (0.278) Hematopoietic/Immune (0.204) Nervous (0.148)	Cell Proliferative (0.777) Inflammation (0.222)	pINCY
70	759-803	Reproductive (0.261) Gastrointestinal (0.217) Nervous (0.174)	Cell Proliferative (0.565) Trauma (0.130)	pINCY
71	110-154	Nervous (0.250) Developmental (0.208) Gastrointestinal (0.167)	Cell Proliferative (0.583) Trauma (0.167)	pINCY
72	529-573	Reproductive (0.186) Gastrointestinal (0.168) Hematopoietic/Immune (0.138)	Cell Proliferative (0.700) Inflammation (0.251)	pINCY
73	1784-1828	Reproductive (0.286) Hematopoietic/Immune (0.190) Nervous (0.167)	Cell Proliferative (0.667) Inflammation (0.286)	PSPORT1
74	111-155	Reproductive (0.316) Nervous (0.211) Hematopoietic/Immune (0.158)	Cell Proliferative (0.632) Inflammation (0.211)	PSPORT1
75	543-587	Reproductive (0.258) Nervous (0.206) Gastrointestinal (0.134)	Cell Proliferative (0.608) Inflammation (0.196)	pINCY

TABLE 3 (cont.)

Nucleotide Seq ID NO:	Selected Fragment	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
76	272-316	Reproductive (0.246) Nervous (0.180) Hematopoietic/Immune (0.148)	Cell Proliferative (0.606) Inflammation (0.279)	pINCY
77	227-271	Hematopoietic/Immune (0.222) Endocrine (0.167) Cardiovascular (0.111)	Cell Proliferative (0.666) Inflammation (0.333)	pINCY
78	487-531	Gastrointestinal (0.375) Reproductive (0.250)	Cell Proliferative (0.500) Inflammation (0.250)	pINCY
79	111-155	Gastrointestinal (0.280) Hematopoietic/Immune (0.240) Reproductive (0.120)	Cell Proliferative (0.640) Inflammation (0.440)	pINCY
80	595-639	Reproductive (0.211) Gastrointestinal (0.158) Urologic (0.158)	Cell Proliferative (0.684) Inflammation (0.263)	pINCY
81	425-469	Reproductive (0.222) Gastrointestinal (0.160) Nervous (0.148)	Cell Proliferative (0.568) Inflammation (0.259)	PSPORT1
82	774-818	Gastrointestinal (0.200) Hematopoietic/Immune (0.200) Nervous (0.200)	Cancer (0.600) Trauma (0.200) Inflammation (0.200)	PBLUESCRIPT
83	517-561	Nervous (0.526) Reproductive (0.132) Cardiovascular (0.105)	Cancer (0.342) Fetal (0.158) Inflammation (0.158)	PBLUESCRIPT
84	1944-1988	Nervous (0.250) Reproductive (0.188) Endocrine (0.125)	Cancer (0.438) Fetal (0.250) Trauma (0.250)	PSPORT1
85	1027-1071	Reproductive (0.219) Nervous (0.206) Hematopoietic/Immune (0.116)	Cancer (0.458) Inflammation (0.232) Fetal (0.181)	PSPORT1

TABLE 3 (cont.)

Nucleotide Seq ID NO:	Selected Fragment	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
86	658-702	Reproductive (0.227) Hematopoietic/Immune (0.182) Gastrointestinal (0.167)	Cancer (0.424) Inflammation (0.318) Fetal (0.167)	PT7T3
87	488-532	Nervous (0.200) Reproductive (0.200) Musculoskeletal (0.120)	Cancer (0.320) Fetal (0.320) Inflammation (0.320)	pINCY
88	379-423	Cardiovascular (0.250) Nervous (0.250) Reproductive (0.250)	Cancer (0.417) Fetal (0.167) Neurological (0.167)	pINCY
89	632-676	Reproductive (0.417) Cardiovascular (0.167) Gastrointestinal (0.167)	Cancer (0.333) Fetal (0.167) Inflammation (0.167)	pINCY
90	258-302	Reproductive (0.294) Nervous (0.137) Hematopoietic/Immune (0.118)	Cancer (0.569) Fetal (0.431) Inflammation (0.176)	pINCY
91	433-477	Reproductive (0.750) Nervous (0.250)	Cancer (0.500) Inflammation (0.500)	PSPORT1
92	542-586	Gastrointestinal (0.273) Hematopoietic/Immune (0.273) Developmental (0.182)	Cancer (0.455) Inflammation (0.364) Fetal (0.182)	pINCY
93	218-262	Reproductive (0.272) Nervous (0.204) Cardiovascular (0.126)	Cancer (0.447) Inflammation (0.214) Fetal (0.155)	PSPORT1
94	541-585	Reproductive (0.273) Nervous (0.250) Cardiovascular (0.159)	Cancer (0.364) Fetal (0.205) Inflammation (0.205)	PSPORT1
95	111-155	Reproductive (0.250) Gastrointestinal (0.173) Nervous (0.154)	Cancer (0.481) Fetal (0.231) Inflammation (0.212)	PSPORT1
96	597-641	Reproductive (0.261) Cardiovascular (0.217) Nervous (0.130)	Cancer (0.391) Fetal (0.304) Inflammation (0.130)	PSPORT1

TABLE 3 (cont.)

Nucleotide Seq ID NO:	Selected Fragment	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
97	434-478	Cardiovascular (0.222) Endocrine (0.222) Gastrointestinal (0.222)	Cancer (0.667) Fetal (0.111) Neurological (0.111)	PSPORT1
98	218-247 920-964	Reproductive (0.333) Gastrointestinal (0.129) Hematopoietic/Immune (0.118)	Cancer (0.559) Inflammation (0.204) Fetal (0.183)	pINCY
99	327-371	Gastrointestinal (0.211) Reproductive (0.211) Cardiovascular (0.158)	Cancer (0.421) Fetal (0.316) Inflammation (0.158)	pINCY
100	596-625	Reproductive (0.230) Nervous (0.164) Gastrointestinal (0.131)	Cancer (0.590) Inflammation (0.246) Fetal (0.082)	PSPORT
101	487-531	Cardiovascular (0.235) Reproductive (0.235) Hematopoietic/Immune (0.176)	Cancer (0.588) Inflammation (0.176) Trauma (0.118)	pINCY
102	218-247 542-586	Gastrointestinal (0.241) Hematopoietic/Immune (0.207) Cardiovascular (0.138)	Cancer (0.448) Fetal (0.276) Inflammation (0.276)	pINCY
103	219-263	Reproductive (0.500) Cardiovascular (0.250) Hematopoietic/Immune (0.250)	Cancer (0.500) Inflammation (0.250) Trauma (0.250)	pINCY
104	111-140 327-371	Hematopoietic/Immune (0.286) Nervous (0.238) Reproductive (0.143)	Cancer (0.333) Fetal (0.286) Inflammation (0.286)	pINCY
105	243-281	Musculoskeletal (0.286) Nervous (0.286) Gastrointestinal (0.143)	Inflammation (0.429) Fetal (0.286) Cancer (0.286)	pINCY
106	271-315	Nervous (0.800) Reproductive (0.100) Cardiovascular (0.100)	Cancer (0.400) Inflammation (0.200) Trauma (0.200)	pINCY

TABLE 3 (cont.)

Nucleotide Seq ID NO:	Selected Fragment	Tissue Expression (Fraction of Total)	Disease or Condition (Fraction of Total)	Vector
107	489-533	Cardiovascular (0.364) Gastrointestinal (0.182) Reproductive (0.182)	Cancer (0.273) Trauma (0.273) Inflammation (0.182)	pINCY
108	156-200	Nervous (0.256) Reproductive (0.256) Hematopoietic/Immune (0.128)	Cancer (0.465) Fetal (0.291) Inflammation (0.186)	pINCY
109	1459-1503	Cardiovascular (0.250) Hematopoietic/Immune (0.250) Nervous (0.167)	Inflammation (0.417) Cancer (0.333) Trauma (0.167)	PSPORT1
110	164-208	Nervous (1.000)	Neurological (1.000)	pINCY

TABLE 4

Nucleotide SEQ ID NO:	Library	Library Comment
56	SPLNFET01	Library was constructed at Stratagene, using RNA isolated from a pool of fetal spleen tissue. Following vector packaging, $2x10^6$ primary clones were then amplified to stabilize the library for long-term storage. Amplification may significantly skew sequence abundances.
57	SYNORAB01	Library was constructed using RNA isolated from the synovial membrane tissue of a 68-year-old Caucasian female with rheumatoid arthritis.
58	KIDNNOT01	Library was constructed using RNA isolated from the kidney tissue of a 64-year-old Caucasian female, who died from an intracranial bleed. Patient history included rheumatoid arthritis and tobacco use.
59	PLACNOB01	Library was constructed using RNA isolated from placenta.
60	HNT2RAT01	Library was constructed at Stratagene (STR937231), using RNA isolated from the hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor). Cells were treated with retinoic acid for 24 hours.
61	EOSIHET02	Library was constructed using RNA isolated from peripheral blood cells apheresed from a 48-year-old Caucasian male. Patient history included hypereosinophilia. The cell population was determined to be greater than 77% eosinophils by Wright's staining.
62	HNT2AGT01	Library was constructed at Stratagene (STR937233), using RNA isolated from the hNT2 cell line (derived from a human teratocarcinoma that exhibited properties characteristic of a committed neuronal precursor). Cells were treated with retinoic acid for 5 weeks and with mitotic inhibitors for two weeks and allowed to mature for an additional 4 weeks in conditioned medium.
63	PROSNOT02	Library was constructed using RNA isolated from the diseased prostate tissue removed from a 50-year-old Caucasian male during a retropubic prostatectomy. Pathology indicated adenofibromatous hyperplasia was present. Pathology for the associated tumor tissue indicated adenocarcinoma Gleason grade 3+3. Patient history included dysuria, carcinoma in situ of prostate, coronary atherosclerosis, and hyperlipidemia.
64	COLNTUT02	Library was constructed using RNA isolated from colon tumor tissue removed from a 75-year-old Caucasian male during a hemicolectomy. Pathology indicated invasive grade 3 adenocarcinoma arising in a tubulovillous adenoma, which was distal to the ileocecal valve in the cecum. The tumor penetrated deeply into the muscularis propria but not through it.

TABLE 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
65	KIDNTUT0 1	Library was constructed using RNA isolated from the kidney tumor tissue removed from an 8-month-old female during nephroureterectomy. Pathology indicated Wilms' tumor (nephroblastoma), which involved 90 percent of the renal parenchyma. Prior to surgery, the patient was receiving heparin anticoagulant therapy.
66	THYRNOT0 3	Library was constructed using RNA isolated from thyroid tissue removed from the left thyroid of a 28-year-old Caucasian female during a complete thyroidectomy. Pathology indicated a small nodule of adenomatous hyperplasia present in the left thyroid. Pathology for the associated tumor tissue indicated dominant follicular adenoma, forming a well-encapsulated mass in the left thyroid.
67	BLADTUT0 4	Library was constructed using RNA isolated from bladder tumor tissue removed from a 60-year-old Caucasian male during a radical cystectomy, prostatectomy, and vasectomy. Pathology indicated grade 3 transitional cell carcinoma in the left bladder wall. Carcinoma in-situ was identified in the dome and trigone. Patient history included tobacco use. Family history included type I diabetes, a malignant neoplasm of the stomach, atherosclerotic coronary artery disease, and an acute myocardial infarction.
68	PROSNOT1 5	Library was constructed using RNA isolated from diseased prostate tissue removed from a 66-year-old Caucasian male during radical prostatectomy and regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 2+3). The patient presented with elevated prostate specific antigen (PSA). Family history included prostate cancer, secondary bone cancer, and benign hypertension.
69	BRSTTUT0 8	Library was constructed using RNA isolated from breast tumor tissue removed from a 45-year-old Caucasian female during unilateral extended simple mastectomy. Pathology indicated invasive nuclear grade 2-3 adenocarcinoma, ductal type, with 3 of 23 lymph nodes positive for metastatic disease. Greater than 50% of the tumor volume was in situ, both comedo and non-comedo types. Immunostains were positive for estrogen/progesterone receptors, and uninvolved tissue showed proliferative changes. The patient concurrently underwent a total abdominal hysterectomy. Patient history included valvuloplasty of mitral valve without replacement, rheumatic mitral insufficiency, and rheumatic heart disease. Family history included acute myocardial infarction, atherosclerotic coronary artery disease, and type II diabetes.

TABLE 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
70	PROSNOT19	Library was constructed using RNA isolated from diseased prostate tissue removed from a 59-year-old Caucasian male during a radical prostatectomy with regional lymph node excision. Pathology indicated adenofibromatous hyperplasia. Pathology for the associated tumor tissue indicated an adenocarcinoma (Gleason grade 3+3). The patient presented with elevated prostate-specific antigen (PSA). Patient history included colon diverticuli, asbestosis, and thrombophlebitis. Previous surgeries included a partial colectomy. Family history included benign hypertension, multiple myeloma, hyperlipidemia and rheumatoid arthritis.
71	THP1NOT03	Library was constructed using RNA isolated from untreated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
72	THP1NOT03	Library was constructed using RNA isolated from untreated THP-1 cells. THP-1 (ATCC TIB 202) is a human promonocyte line derived from the peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia (ref: Int. J. Cancer (1980) 26:171).
73	HIPOAZT01	Library was constructed from RNA isolated from diseased hippocampus tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
74	HIPOAZT01	Library was constructed from RNA isolated from diseased hippocampus tissue removed from the brain of a 74-year-old Caucasian male who died from Alzheimer's disease.
75	BRSTNOT13	Library was constructed using RNA isolated from breast tissue removed from the left medial lateral breast of a 36-year-old Caucasian female during bilateral simple mastectomy and total breast reconstruction. Pathology indicated benign breast tissue. Patient history included a breast neoplasm, depressive disorder, hyperlipidemia, chronic stomach ulcer, and an ectopic pregnancy. Family history included myocardial infarction, cerebrovascular disease, atherosclerotic coronary artery disease, hyperlipidemia, skin cancer, breast cancer, depressive disorder, esophageal cancer, bone cancer, Hodgkin's lymphoma, bladder cancer, and heart condition.
76	NPOLNOT01	Library was constructed using RNA isolated from nasal polyp tissue removed from a 78-year-old Caucasian male during a nasal polypectomy. Pathology indicated a nasal polyp and striking eosinophilia. Patient history included asthma and nasal polyps.

TABLE 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
77	ADRENOT09	Library was constructed using RNA isolated from left adrenal gland tissue removed from a 43-year-old Caucasian male during nephroureterectomy, regional lymph node excision, and unilateral left adrenalectomy. Pathology indicated no diagnostic abnormalities of the adrenal gland. Pathology for the associated tumor tissue indicated a grade 2 renal cell carcinoma mass in the posterior lower pole of the left kidney with invasion into the renal pelvis.
78	SPLNNOT11	Library was constructed using RNA isolated from diseased spleen tissue removed from a 14-year-old Asian male during a total splenectomy. Pathology indicated changes consistent with idiopathic thrombocytopenic purpura. The patient presented with bruising.
79	CONCNOT01	Library was constructed using RNA isolated from chest wall soft tissue removed from a 63-year-old Caucasian male during a chest wall lesion destruction. Pathology indicated surgical margins were free of tumor. Pathology for the associated tumor tissue indicated invasive grade 3 adenocarcinoma, forming a mass that extended through the visceral pleura to involve parietal pleura. Patient history included MEN (multiple endocrine neoplasia) syndrome type I, abnormal secretion of gastrin, alcohol and tobacco abuse, calcium metabolism disease, chronic stomach ulcer with hemorrhage, lung cancer, and calculus of the kidney. Family history included prostate cancer, benign hypertension, stroke, atherosclerotic coronary artery disease, type II diabetes, hyperlipidemia, and cancer of an unspecified location.
80	TONSNOT03	Library was constructed using RNA isolated from diseased left tonsil tissue removed from a 6-year-old Caucasian male during adenotonsillectomy. Pathology indicated reactive lymphoid hyperplasia, bilaterally. Family history included benign hypertension, myocardial infarction, and atherosclerotic coronary artery disease.
81	LUNGNON03	This normalized library was constructed from 2.56×10^6 independent clones from a lung tissue library. RNA was made from lung tissue removed from the left lobe a 58-year-old Caucasian male during a segmental lung resection. Pathology for the associated tumor tissue indicated a metastatic grade 3 (of 4) osteosarcoma. Patient history included soft tissue cancer, secondary cancer of the lung, prostate cancer, and an acute duodenal ulcer with hemorrhage. Patient also received radiation therapy to the retroperitoneum. Family history included prostate cancer, breast cancer, and acute leukemia. The normalization and hybridization conditions were adapted from Soares et al., PNAS (1994) 91:9228; Swaroop et al., NAR (1991) 19:1954; and Bonaldo et al., Genome Research (1996) 6:791.

TABLE 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
82	BMARNOT0 2	The library was constructed using Clontech RNA isolated from the bone marrow of 24 male and female Caucasian donors, 16 to 70 years old.
83	SINTNOT0 2	The library was constructed using RNA isolated from the small intestine of a 55-year-old Caucasian female, who died from a subarachnoid hemorrhage. Serologies were positive for cytomegalovirus (CMV).
84	CRBLNOT0 1	The library was constructed using RNA isolated from the cerebellum tissue of a 69-year-old Caucasian male who died from chronic obstructive pulmonary disease. Patient history included myocardial infarction, hypertension, and osteoarthritis.
85	BRSTNOT0 3	The library was constructed using RNA isolated from diseased breast tissue removed from a 54-year-old Caucasian female during a bilateral radical mastectomy. Pathology for the associated tumor tissue indicated residual invasive grade 3 mammary ductal adenocarcinoma. Patient history included kidney infection and condyloma acuminatum. Family history included benign hypertension, hyperlipidemia and a malignant neoplasm of the colon.
86	BEPINON0 1	The normalized bronchial epithelium library was constructed from 5.12 million independent clones from a bronchial epithelium library. RNA was isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male. The normalization and hybridization conditions were adapted from Soares et al., PNAS (1994) 91:9228, using a 24-hour reannealing hybridization period.
87	THYRNOT0 3	The library was constructed using RNA isolated from thyroid tissue removed from the left thyroid of a 28-year-old Caucasian female during a complete thyroidectomy. Pathology indicated a small nodule of adenomatous hyperplasia present in the left thyroid. Pathology for the associated tumor tissue indicated dominant follicular adenoma, forming a well-encapsulated mass in the left thyroid.
88	COLNFET0 2	The library was constructed using RNA isolated from the colon tissue of a Caucasian female fetus who died at 20 weeks' gestation.
89	BLADNOT0 3	The library was constructed using RNA isolated from bladder tissue removed from an 80-year-old Caucasian female during a radical cystectomy and lymph node excision. Pathology for the associated tumor tissue indicated grade 3 invasive transitional cell carcinoma. Patient history included malignant neoplasm of the uterus, atherosclerosis, and atrial fibrillation. Family history included acute renal failure, osteoarthritis, and atherosclerosis.

TABLE 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
90	COLNNOT23	The library was constructed using RNA isolated from diseased colon tissue removed from a 16-year-old Caucasian male during a total colectomy with abdominal/perineal resection. Pathology indicated gastritis and pancolonitis consistent with the acute phase of ulcerative colitis. Inflammation was more severe in the transverse colon with inflammation confined to the mucosa. The ascending and sigmoid colon was mildly involved. Family history included irritable bowel syndrome.
91	BRSTNOT04	The library was constructed using RNA isolated from breast tissue removed from a 62-year-old East Indian female during a unilateral extended simple mastectomy. Pathology for the associated tumor tissue indicated an invasive grade 3 ductal carcinoma. Patient history included benign hypertension, hyperlipidemia, and hematuria. Family history included cerebrovascular and cardiovascular disease, hyperlipidemia, and liver cancer.
92	LIVRFET02	The library was constructed using RNA isolated from liver tissue removed from a Caucasian female fetus who died at 20 weeks' gestation. Family history included seven days of erythromycin treatment for bronchitis in the mother during the first trimester.
93	BEPINOT01	The library was constructed using RNA isolated from a bronchial epithelium primary cell line derived from a 54-year-old Caucasian male.
94	BRAITUT02	The library was constructed using RNA isolated from brain tumor tissue removed from the frontal lobe of a 58-year-old Caucasian male during excision of a cerebral meningeal lesion. Pathology indicated a grade 2 metastatic hypernephroma. Patient history included a grade 2 renal cell carcinoma, insomnia, and chronic airway obstruction. Family history included a malignant neoplasm of the kidney.
95	BRAITUT03	The library was constructed using RNA isolated from brain tumor tissue removed from the left frontal lobe a 17-year-old Caucasian female during excision of a cerebral meningeal lesion. Pathology indicated a grade 4 fibrillary giant and small-cell astrocytoma. Family history included benign hypertension and cerebrovascular disease.
96	BRSTTUT02	The library was constructed using RNA isolated from breast tumor tissue removed from a 54-year-old Caucasian female during a bilateral radical mastectomy with reconstruction. Pathology indicated residual invasive grade 3 mammary ductal adenocarcinoma. The remaining breast parenchyma exhibited proliferative fibrocystic changes without atypia. One of 10 axillary lymph nodes had metastatic tumor. Patient history included kidney infection and condyloma acuminatum. Family history included benign hypertension, hyperlipidemia, and a malignant colon neoplasm.

TABLE 4 (cont.)

Nucleotide SEQ ID NO:	Library	Library Comment
97	BRSTTUT02	The library was constructed using RNA isolated from breast tumor tissue removed from a 54-year-old Caucasian female during a bilateral radical mastectomy with reconstruction. Pathology indicated residual invasive grade 3 mammary ductal adenocarcinoma. The remaining breast parenchyma exhibited proliferative fibrocystic changes without atypia. One of 10 axillary lymph nodes had metastatic tumor. Patient history included kidney infection and condyloma acuminatum. Family history included benign hypertension, hyperlipidemia, and a malignant colon neoplasm.
98	BRSTNOT07	The library was constructed using RNA isolated from diseased breast tissue removed from a 43-year-old Caucasian female during a unilateral extended simple mastectomy. Pathology indicated mildly proliferative fibrocystic changes with epithelial hyperplasia, papillomatosis, and duct ectasia. Pathology for the associated tumor tissue indicated invasive grade 4, nuclear grade 3 mammary adenocarcinoma with extensive comedo necrosis. Family history included epilepsy, cardiovascular disease, and type II diabetes.
99	BRAINOT09	The library was constructed using RNA isolated from brain tissue removed from a Caucasian male fetus who died at 23 weeks' gestation.
100	THP1AZS08	The library was constructed using RNA isolated from 5.76 million clones from a 5-aza-2'-deoxycytidine treated THP-1 cell library. The library was subjected to subtractive hybridization using 5 million clones from an untreated THP-1 cell library. Hybridization conditions were adapted from Swaroop et al., NAR (1991) 19:1954; and Bonaldo et al., Genome Research (1996) 6:791. THP-1 (ATCC TIB 202) is a human promonocyte cell line derived from peripheral blood of a 1-year-old Caucasian male with acute monocytic leukemia.
101	LUNGTUT12	The library was constructed using RNA isolated from tumorous lung tissue removed from a 70-year-old Caucasian female during a lung lobectomy of the left upper lobe. Pathology indicated grade 3 (of 4) adenocarcinoma and vascular invasion. Patient history included tobacco abuse, depressive disorder, anxiety state, and skin cancer. Family history included cerebrovascular disease, congestive heart failure, colon cancer, depressive disorder, and primary liver.
102	HEAONOT05	The library was constructed using RNA isolated from aortic tissue removed from a 17-year-old Hispanic female who died from a gunshot wound.
103	HEAONOT05	The library was constructed using RNA isolated from aortic tissue removed from a 17-year-old Hispanic female who died from a gunshot wound.

Table 5

Program	Description	Reference	Parameter Threshold
ABI FACTURA	A program that removes vector sequences and masks ambiguous bases in nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
ABI/PARACEL FDF	A Fast Data Finder useful in comparing and annotating amino acid or nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA; Paracel Inc., Pasadena, CA.	Mismatch <50%
ABI AutoAssembler	A program that assembles nucleic acid sequences.	Perkin-Elmer Applied Biosystems, Foster City, CA.	
BLAST	A Basic Local Alignment Search Tool useful in sequence similarity search for amino acid and nucleic acid sequences. BLAST includes five functions: blastp, blastn, blastx, tblastn, and tblastx.	Altschul, S.F. et al. (1990) J. Mol. Biol. 215:403-410; Altschul, S.F. et al. (1997) Nucleic Acids Res. 25: 3389-3402.	*ESTs:* Probability value= 1.0E-8 o less *Full Length sequences*: Probability value= 1.0E-10 or less
FASTA	A Pearson and Lipman algorithm that searches for similarity between a query sequence and a group of sequences of the same type. FASTA comprises as least five functions: fasta, tfasta, fastx, tfastx, and ssearch.	Pearson, W.R. and D.J. Lipman (1988) Proc. Natl. Acad Sci. 85:2444-2448; Pearson, W.R. (1990) Methods Enzymol. 183: 63-98; and Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489.	*ESTs:* fasta E value=1.06E-6 *Assembled ESTs*: fasta Identity= 95% or greater and Match length=200 bases or greater. fastx E value=1.0E-8 or less *Full Length sequences:* fastx score=100 or greater
BLIMPS	A BLocks IMProved Searcher that matches a sequence against those in BLOCKS, PRINTS, DOMO, PRODOM, and PFAM databases to search for gene families, sequence homology, and structural fingerprint regions.	Henikoff, S and J.G. Henikoff, Nucl. Acid Res., 19:6565-72, 1991. J.G. Henikoff and S. Henikoff (1996) Methods Enzymol. 266:88-105; and Attwood, T.K. et al. (1997) J. Chem. Inf. Comput. Sci. 37: 417-424.	Score=1000 or greater; Ratio of Score/Strength = 0.75 or larger; and, if applicable, Probability value= 1.0E-3 or less
HMMER	An algorithm for searching a query sequence against hidden Markov model (HMM)-based databases of protein family consensus sequences, such as PFAM.	Krogh, A. et al. (1994) J. Mol. Biol., 235:1501-1531; Sonnhammer, E.L.L. et al. (1988) Nucleic Acids Res. 26:320-322.	Score=10-50 bits for PFAM hits, depending on individual protein families

Table 5 (cont.)

Program	Description	Reference	Parameter Threshold
ProfileScan	An algorithm that searches for structural and sequence motifs in protein sequences that match sequence patterns defined in Prosite.	Gribskov, M. et al. (1988) CABIOS 4:61-66; Gribskov, et al. (1989) Methods Enzymol. 183:146-159; Bairoch, A. et al. (1997) Nucleic Acids Res. 25: 217-221.	Normalized quality score≥GCG-specified "HIGH" value for that particular Prosite motif. Generally, score=1.4-2.1.
Phred	A base-calling algorithm that examines automated sequencer traces with high sensitivity and probability.	Ewing, B. et al. (1998) Genome Res. 8:175-185; Ewing, B. and P. Green (1998) Genome Res. 8:186-194.	
Phrap	A Phils Revised Assembly Program including SWAT and CrossMatch, programs based on efficient implementation of the Smith-Waterman algorithm, useful in searching sequence homology and assembling DNA sequences.	Smith, T.F. and M. S. Waterman (1981) Adv. Appl. Math. 2:482-489; Smith, T.F. and M. S. Waterman (1981) J. Mol. Biol. 147:195-197; and Green, P., University of Washington, Seattle, WA.	Score= 120 or greater; Match length= 56 or greater
Consed	A graphical tool for viewing and editing Phrap assemblies	Gordon, D. et al. (1998) Genome Res. 8:195-202.	
SPScan	A weight matrix analysis program that scans protein sequences for the presence of secretory signal peptides.	Nielson, H. et al. (1997) Protein Engineering 10:1-6; Claverie, J.M. and S. Audic (1997) CABIOS 12: 431-439.	Score=3.5 or greater
Motifs	A program that searches amino acid sequences for patterns that matched those defined in Prosite.	Bairoch et al. supra; Wisconsin Package Program Manual, version 9, page M51-59, Genetics Computer Group, Madison, WI.	

What is claimed is:

1. An isolated polypeptide comprising:

a) an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3-5, SEQ ID NO:7-14, SEQ ID NO:16-31, SEQ ID NO:33-34, SEQ ID NO:36-40,SEQ ID NO:42-48, SEQ ID NO:50-55.

b) a naturally occurring amino acid sequence having at least 90% sequence identity to an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3-5, SEQ ID NO:7-14, SEQ ID NO:16-31, SEQ ID NO:33-34, SEQ ID NO:36-40,SEQ ID NO:42-48, SEQ ID NO:50-55,

c) a biologically active fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3-5, SEQ ID NO:7-14, SEQ ID NO:16-31, SEQ ID NO:33-34, SEQ ID NO:36-40,SEQ ID NO:42-48, SEQ ID NO:50-55, or

d) an immunogenic fragment of an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3-5, SEQ ID NO:7-14, SEQ ID NO:16-31, SEQ ID NO:33-34, SEQ ID NO:36-40,SEQ ID NO:42-48, SEQ ID NO:50-55.

2. An isolated polypeptide of claim 1, having an amino acid sequence selected from the group consisting of SEQ ID NO:1, SEQ ID NO:3-5, SEQ ID NO:7-14, SEQ ID NO:16-31, SEQ ID NO:33-34, SEQ ID NO:36-40,SEQ ID NO:42-48, SEQ ID NO:50-55.

3. An isolated polynucleotide encoding a polypeptide of claim 1.

4. An isolated polynucleotide of claim 3, having a sequence selected from the group consisting of SEQ ID NO:56-110.

5. A recombinant polynucleotide comprising a promoter sequence operably linked to a polynucleotide of claim 3.

6. A cell transformed with a recombinant polynucleotide of claim 5.

7. A transgenic organism comprising a polynucleotide of claim 5.

8. A method for producing a polypeptide of claim 1, the method comprising:

a) culturing a cell under conditions suitable for expression of the polypeptide, wherein said

cell is transformed with a recombinant polynucleotide, and said recombinant polynucleotide comprises a promoter sequence operably linked to a polynucleotide encoding the polypeptide of claim 1, and

b) recovering the polypeptide so expressed.

9. An isolated antibody which specifically binds to a polypeptide of claim 1.

10. An isolated polynucleotide comprising:

a) a polynucleotide sequence selected from the group consisting of SEQ ID NO:56-110,

b) a naturally occurring polynucleotide sequence having at least 90% sequence identity to a polynucleotide sequence selected from the group consisting of SEQ ID NO:56-110,

c) a polynucleotide sequence complementary to a), or

d) a polynucleotide sequence complementary to b).

11. An isolated polynucleotide comprising at least 60 contiguous nucleotides of a polynucleotide of claim 10.

12. A method for detecting a target polynucleotide in a sample, said target polynucleotide having a sequence of a polynucleotide of claim 10, the method comprising:

a) hybridizing the sample with a probe comprising at least 16 contiguous nucleotides comprising a sequence complementary to said target polynucleotide in the sample, and which probe specifically hybridizes to said target polynucleotide, under conditions whereby a hybridization complex is formed between said probe and said target polynucleotide, and

b) detecting the presence or absence of said hybridization complex, and, optionally, if present, the amount thereof.

13. A method of claim 12, wherein the probe comprises at least 30 contiguous nucleotides.

14. A method of claim 12, wherein the probe comprises at least 60 contiguous nucleotides.

15. A pharmaceutical composition comprising an effective amount of a polypeptide of claim 1 and a pharmaceutically acceptable excipient.

16. A method of treating a disease or condition associated with decreased expression of

functional NuABP, comprising administering to a patient in need of such treatment the pharmaceutical composition of claim 15.

17. A method for screening a compound for effectiveness as an agonist of a polypeptide of claim 1, the method comprising:

a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting agonist activity in the sample.

18. A pharmaceutical composition comprising an agonist compound identified by a method of claim 17 and a pharmaceutically acceptable excipient.

19. A method of treating a disease or condition associated with decreased expression of functional NuABP, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 18.

20. A method for screening a compound for effectiveness as an antagonist of a polypeptide of claim 1, the method comprising:

a) exposing a sample comprising a polypeptide of claim 1 to a compound, and

b) detecting antagonist activity in the sample.

21. A pharmaceutical composition comprising an antagonist compound identified by a method of claim 20 and a pharmaceutically acceptable excipient.

22. A method for treating a disease or condition associated with overexpression of functional NuABP, comprising administering to a patient in need of such treatment a pharmaceutical composition of claim 21.

23. A method for screening a compound for effectiveness in altering expression of a target polynucleotide, wherein said target polynucleotide comprises a sequence of claim 4, the method comprising:

a) exposing a sample comprising the target polynucleotide to a compound, and

b) detecting altered expression of the target polynucleotide.

SEQUENCE LISTING

<110> INCYTE PHARMACEUTICALS, INC.
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BAUGHN, Mariah R.
TRAN, Bao
SHIH, Leo L.
AU-YOUNG, Janice

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<130> PF-0662 PCT

<140> To Be Assigned
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<150> 60/117,905; 60/117,904
<151> 1999-01-29; 1999-01-29

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Cys Phe Ile Ile Phe Glu Asp Ser Ser Lys Ser Trp Val Leu Trp
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                155                 160                 165
Leu Lys Lys Gly Pro Asn Ala Lys Ala Leu Gln Val Met Lys Gln
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Thr Leu Pro Tyr Ser Val Ala Asp Leu Glu Trp Asp Ala Gly His
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Pro Glu Tyr Leu Lys Arg Leu Pro Leu Gln Trp Val Asp Ile Ala
                260                 265                 270
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                275                 280                 285
Phe Asp Ser Glu Leu Glu Leu Met Thr Tyr Ile Asn Glu Asn Trp
                290                 295                 300
Asp Arg Leu His Pro Gly Glu Leu Ala Asp Thr Pro Lys Ser Glu
                305                 310                 315
Arg Tyr Glu His Val Leu Glu Ala Leu Asn Asp Tyr Lys Thr Met
                320                 325                 330
Phe Met Ser Gly Lys Glu Ile Lys Lys Lys Lys His Leu Phe Gly
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Leu Arg Ile Arg Val Pro Pro Val Pro Pro Asn Val Ala Phe Lys
                350                 355                 360
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Asn Gly Ile Glu Lys Lys Lys Lys Lys Lys Ser Val Gly Arg Pro
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Pro Gly Pro Tyr Thr Arg Lys Met Ile Gln Lys Thr Ala Glu Pro
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Thr Ser Asp Val Asp Phe Thr Gly Ala Ser Ser Ala Lys Glu Thr
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Thr Ser Ser Ser Ile Ser Arg His Tyr Gly Leu Ser Asp Ser Arg
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            185                 190                 195
Val Asn Gly Lys Leu Phe Pro Leu Pro Gly Tyr Ala Pro Pro Pro
            200                 205                 210
Lys Asn Gly Ile Glu Gln Lys Arg Pro Gly Arg Pro Leu Asn Ile
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Thr Ser Leu Val Arg Leu Ser Ser Ala Val Pro Asn Gln Ile Ser
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            335                 340                 345
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            380                 385                 390
Pro Lys Lys Glu Ala Met Lys Val Ser Ser Gln Pro Cys Thr Lys
            395                 400                 405
Ile Glu Ser Ser Ser Val Leu Ser Lys Pro Cys Ser Val Thr Val
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            425                 430                 435
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                485                 490                 495
Val Pro Phe His His Thr Pro Ile Ser Ser Met Ser Ser Asp Leu
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185 190 195
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200 205 210
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230 235 240
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320 325 330
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335 340 345
Met Val Ser Tyr Cys Gln Asn Ile Ser Lys Cys Arg Arg Val Leu
350 355 360
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Val Ala Pro Thr Leu Pro Arg Glu Asp Leu Glu Lys Ile Ile Ala
                440                 445                 450
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                455                 460                 465
Ala Tyr Ala Thr Ile Ser Tyr Leu Lys Ile Gly Pro Lys Ala Asn
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Ser Thr Gln Asn Ser Phe Arg Ala Glu Ser Ser Gln Thr Cys His
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Ser Glu Gln Gly Asp Lys Lys Ile Gly Gly Lys Lys Phe Gln Ala
                515                 520                 525
Thr Ser Arg Arg Arg Leu Gln Thr Cys Phe Ser Asn Leu Val Leu
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                 50                  55                  60
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                 80                  85                  90
Glu Leu Gly Ala Pro Pro Lys His Gly Lys Pro Lys Lys Gln Lys
                 95                 100                 105
Leu Glu Gly Lys Ala Gly His Gly Pro Gly Pro Gly Pro Gly Arg
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                170                 175                 180
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                185                 190                 195
Tyr Ser Gln Arg Trp Ala Gln Glu Asp Leu Leu Glu Glu Gln Lys
                200                 205                 210
Asp Gly Ala Arg Ala Ala Ala Val Ala Asp Lys Lys Lys Gly Leu
                215                 220                 225
Met Gly Pro Leu Thr Glu Leu Asp Thr Lys Asp Val Asp Ala Leu
                230                 235                 240
Leu Lys Lys Ser Glu Ala Gln His Glu Gln Pro Glu Asp Gly Cys
                245                 250                 255
Pro Phe Gly Ala Leu Thr Gln Arg Leu Leu Gln Ala Leu Val Glu
                260                 265                 270
Glu Asn Ile Ile Ser Pro Met Glu Asp Ser Pro Ile Pro Asp Met
                275                 280                 285
Ser Gly Lys Glu Ser Gly Ala Asp Gly Ala Ser Thr Ser Pro Arg
                290                 295                 300
Asn Gln Asn Lys Pro Phe Ser Val Pro His Thr Lys Ser Leu Glu
                305                 310                 315
Ser Arg Ile Lys Glu Glu Leu Ile Ala Gln Gly Leu Leu Glu Ser
                320                 325                 330
Glu Asp Arg Pro Ala Glu Asp Ser Glu Asp Glu Val Leu Ala Glu
                335                 340                 345
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                350                 355                 360
Arg Thr Lys Lys His Asp Leu Leu Arg Leu Ala Lys Glu Glu Val
                365                 370                 375
Ser Arg Gln Glu Leu Arg Gln Arg Val Arg Met Ala Asp Asn Glu
                380                 385                 390
Val Met Asp Ala Phe Arg Lys Ile Met Ala Ala Arg Gln Lys Lys
                395                 400                 405
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                35                  40                  45
Lys Leu Tyr Arg Asp Val Met Val Glu Asn Phe Lys Asn Leu Val
                50                  55                  60
Ala Val Gly His Leu Pro Phe Gln Pro Asp Met Val Ser Gln Leu
                65                  70                  75
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                 95                 100                 105
Leu Lys Tyr Leu Ser Asn Gln Glu Leu Ser Cys Trp Gln Ile Trp
                110                 115                 120
Lys Gln Val Ala Ser Glu Leu Thr Arg Cys Leu Gln Gly Lys Ser
                125                 130                 135
Ser Gln Leu Leu Gln Gly Asp Ser Ile Gln Val Ser Glu Asn Glu
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Asn Asn Ile Met Asn Pro Lys Gly Asp Ser Pro Ile Tyr Ile Glu
                155                 160                 165
Asn Gln Glu Phe Pro Phe Trp Arg Thr Gln His Ser Cys Gly Asn
                170                 175                 180
Thr Tyr Leu Ser Glu Ser Gln Ile Gln Ser Arg Gly Lys Gln Ile
                185                 190                 195
Asp Val Lys Asn Asn Leu Gln Ile Arg Glu Asp Phe Val Lys Lys
                200                 205                 210
Ser Pro Phe His Glu His Ile Lys Thr Asp Thr Glu Pro Lys Pro
                215                 220                 225
Cys Lys Gly Asn Glu Tyr Gly Lys Ile Ile Ser Asp Gly Ser Asn
                230                 235                 240
Gln Lys Leu Pro Leu Gly Glu Lys Pro His Pro Cys Gly Glu Cys
                245                 250                 255
Gly Arg Gly Phe Ser Tyr Ser Pro Arg Leu Pro Leu His Pro Asn
                260                 265                 270
Val His Thr Gly Glu Lys Cys Phe Ser Gln Ser Ser His Leu Arg
                275                 280                 285
Thr His Gln Arg Ile His Pro Gly Glu Lys Leu Asn Arg Cys His
                290                 295                 300
Glu Ser Gly Asp Cys Phe Asn Lys Ser Ser Phe His Ser Tyr Gln
                305                 310                 315
Ser Asn His Thr Gly Glu Lys Ser Tyr Arg Cys Asp Ser Cys Gly
                320                 325                 330
Lys Gly Phe Ser Ser Ser Thr Gly Leu Ile Ile His Tyr Arg Thr
                335                 340                 345
His Thr Gly Glu Lys Pro Tyr Lys Cys Glu Glu Cys Gly Lys Cys
                350                 355                 360
Phe Ser Gln Ser Ser Asn Phe Gln Cys His Gln Arg Val His Thr
                365                 370                 375
Glu Glu Lys Pro Tyr Lys Cys Glu Glu Cys Gly Lys Gly Phe Gly
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Trp Ser Val Asn Leu Arg Val His Gln Arg Val His Arg Gly Glu
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Lys Pro Tyr Lys Cys Glu Glu Cys Gly Lys Gly Phe Thr Gln Ala
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                440                 445                 450
Leu Ile Cys His Arg Arg Val His Thr Gly Glu Lys Pro Tyr Lys
                455                 460                 465

Cys Glu Ala Cys Gly Lys Gly Phe Thr Arg Asn Thr Asp Leu His
                470                 475                 480
Ile His Phe Arg Val His Thr Gly Glu Lys Pro Tyr Lys Cys Lys
                485                 490                 495
Glu Cys Gly Lys Gly Phe Ser Gln Ala Ser Asn Leu Gln Val His
                500                 505                 510
Gln Asn Val His Thr Gly Glu Lys Arg Phe Lys Cys Glu Thr Cys
                515                 520                 525
Gly Lys Gly Phe Ser Gln Ser Ser Lys Leu Gln Thr His Gln Arg
```

```
                530                 535                 540
Val His Thr Gly Glu Lys Pro Tyr Arg Cys Asp Val Cys Gly Lys
                545                 550                 555
Asp Phe Ser Tyr Ser Ser Asn Leu Lys Leu His Gln Val Ile His
                560                 565                 570
Thr Gly Glu Lys Pro Tyr Lys Cys Glu Glu Cys Gly Lys Gly Phe
                575                 580                 585
Ser Trp Arg Ser Asn Leu His Ala His Gln Arg Val His Ser Gly
                590                 595                 600
Glu Lys Pro Tyr Lys Cys Glu Gln Cys Asp Lys Ser Phe Ser Gln
                605                 610                 615
Ala Ile Asp Phe Arg Val His Gln Arg Val His Thr Gly Glu Lys
                620                 625                 630
Pro Tyr Lys Cys Gly Val Cys Gly Lys Gly Phe Ser Gln Ser Ser
                635                 640                 645
Gly Leu Gln Ser His Gln Arg Val His Thr Gly Glu Lys Pro Tyr
                650                 655                 660
Lys Cys Asp Val Cys Gly Lys Gly Phe Arg Tyr Ser Ser Gln Phe
                665                 670                 675
Ile Tyr His Gln Arg Gly His Thr Gly Glu Lys Pro Tyr Lys Cys
                680                 685                 690
Glu Glu Cys Gly Lys Gly Phe Gly Arg Ser Leu Asn Leu Arg His
                695                 700                 705
His Gln Arg Val His Thr Gly Glu Lys Pro His Ile Cys Glu Glu
                710                 715                 720
Cys Gly Lys Ala Phe Ser Leu Pro Ser Asn Leu Arg Val His Leu
                725                 730                 735
Gly Val His Thr Arg Glu Lys Leu Phe Lys Cys Glu Glu Cys Gly
                740                 745                 750
Lys Gly Phe Ser Gln Ser Ala Arg Leu Glu Ala His Gln Arg Val
                755                 760                 765
His Thr Gly Glu Lys Pro Tyr Lys Cys Asp Ile Cys Asp Lys Asp
                770                 775                 780
Phe Arg His Arg Ser Arg Leu Thr Tyr His Gln Lys Val His Thr
                785                 790                 795
Gly Lys Lys Leu
```

<210> 8
<211> 137
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 585172CD1

<400> 8

```
Met Leu Ser Gly Arg Leu Val Leu Gly Leu Val Ser Met Ala Gly
  1                 5                  10                  15
Arg Val Cys Leu Cys Gln Gly Ser Ala Gly Ser Gly Ala Ile Gly
                20                  25                  30
Pro Val Glu Ala Ala Ile Arg Thr Lys Leu Glu Glu Ala Leu Ser
                35                  40                  45
Pro Glu Val Leu Glu Leu Arg Asn Glu Ser Gly Gly His Ala Val
                50                  55                  60

Pro Pro Gly Ser Glu Thr His Phe Arg Val Ala Val Val Ser Ser
                65                  70                  75
Arg Phe Glu Gly Leu Ser Pro Leu Gln Arg His Arg Leu Val His
```

```
                  80                  85                  90
Ala Ala Leu Ala Glu Glu Leu Gly Gly Pro Val His Ala Leu Ala
                  95                 100                 105
Ile Gln Ala Arg Thr Pro Ala Gln Trp Arg Glu Asn Ser Gln Leu
                 110                 115                 120
Asp Thr Ser Pro Pro Cys Leu Gly Gly Asn Lys Lys Thr Leu Gly
                 125                 130                 135
Thr Pro
```

<210> 9
<211> 230
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 615200CD1

<400> 9

```
Met Val Gly Ala Gly Ile Ser Thr Pro Ser Gly Ile Pro Asp Phe
  1               5                  10                  15
Arg Ser Pro Gly Ser Gly Leu Tyr Ser Asn Leu Gln Gln Tyr Asp
                 20                  25                  30
Leu Pro Tyr Pro Glu Ala Ile Phe Glu Leu Pro Phe Phe Phe His
                 35                  40                  45
Asn Pro Lys Pro Phe Phe Thr Leu Ala Lys Glu Leu Tyr Pro Gly
                 50                  55                  60
Asn Tyr Lys Pro Asn Ile Thr His Tyr Phe Leu Arg Leu Leu His
                 65                  70                  75
Asp Lys Gly Leu Leu Leu Arg Leu Tyr Thr Gln Asn Ile Asp Gly
                 80                  85                  90
Leu Glu Arg Val Ser Gly Ile Pro Ala Ser Lys Leu Val Glu Ala
                 95                 100                 105
His Gly Thr Phe Ala Ser Ala Thr Cys Thr Val Cys Gln Arg Pro
                110                 115                 120
Phe Pro Gly Glu Asp Ile Arg Ala Asp Val Met Ala Asp Arg Val
                125                 130                 135
Pro Arg Cys Pro Val Cys Thr Gly Val Val Lys Pro Asp Ile Val
                140                 145                 150
Phe Phe Gly Glu Pro Leu Pro Gln Arg Phe Leu Leu His Val Val
                155                 160                 165
Asp Phe Pro Met Ala Asp Leu Leu Leu Ile Leu Gly Thr Ser Leu
                170                 175                 180
Glu Val Glu Pro Phe Ala Ser Leu Thr Glu Ala Val Arg Thr Gln
                185                 190                 195
Phe Pro Asp Cys Ser Ser Thr Gly Thr Trp Trp Gly Pro Trp Leu
                200                 205                 210
Gly Ile Leu Ala Ala Gly Thr Trp Pro Ser Trp Gly Thr Trp Phe
                215                 220                 225
Thr Ala Trp Lys Ala
                230
```

<210> 10
<211> 446
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 997067CD1

<400> 10
Met Glu Thr Gln Ala Asp Leu Val Ser Gln Glu Pro Gln Ala Leu
1 5 10 15
Leu Asp Ser Ala Leu Pro Ser Lys Val Pro Ala Phe Ser Asp Lys
20 25 30
Asp Ser Leu Gly Asp Glu Met Leu Ala Ala Ala Leu Leu Lys Ala
35 40 45
Lys Ser Gln Glu Leu Val Thr Phe Glu Asp Val Ala Val Tyr Phe
50 55 60
Ile Arg Lys Glu Trp Lys Arg Leu Glu Pro Ala Gln Arg Asp Leu
65 70 75
Tyr Arg Asp Val Met Leu Glu Asn Tyr Gly Asn Val Phe Ser Leu
80 85 90
Asp Arg Glu Thr Arg Thr Glu Asn Asp Gln Glu Ile Ser Glu Asp
95 100 105
Thr Arg Ser His Gly Val Leu Leu Gly Arg Phe Gln Lys Asp Ile
110 115 120
Ser Gln Gly Leu Lys Phe Lys Glu Ala Tyr Glu Arg Glu Val Ser
125 130 135
Leu Lys Arg Pro Leu Gly Asn Ser Pro Gly Glu Arg Leu Asn Arg
140 145 150
Lys Met Pro Asp Phe Gly Gln Val Thr Val Glu Glu Lys Leu Thr
155 160 165
Pro Arg Gly Glu Arg Ser Glu Lys Tyr Asn Asp Phe Gly Asn Ser
170 175 180
Phe Thr Val Asn Ser Asn Leu Ile Ser His Gln Arg Leu Pro Val
185 190 195
Gly Asp Arg Pro His Lys Cys Asp Glu Cys Ser Lys Ser Phe Asn
200 205 210
Arg Thr Ser Asp Leu Ile Gln His Gln Arg Ile His Thr Gly Glu
215 220 225
Lys Pro Tyr Glu Cys Asn Glu Cys Gly Lys Ala Phe Ser Gln Ser
230 235 240
Ser His Leu Ile Gln His Gln Arg Ile His Thr Gly Glu Lys Pro
245 250 255
Tyr Glu Cys Ser Asp Cys Gly Lys Thr Phe Ser Cys Ser Ser Ala
260 265 270
Leu Ile Leu His Arg Arg Ile His Thr Gly Glu Lys Pro Tyr Glu
275 280 285
Cys Asn Glu Cys Gly Lys Thr Phe Ser Trp Ser Ser Thr Leu Thr
290 295 300
His His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Ala Cys Asn
305 310 315
Glu Cys Gly Lys Ala Phe Ser Arg Ser Ser Thr Leu Ile His His
320 325 330
Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Asn Glu Cys
335 340 345
Gly Lys Ala Phe Ser Gln Ser Ser His Leu Tyr Gln His Gln Arg
350 355 360
Ile His Thr Gly Glu Lys Pro Tyr Glu Cys Met Glu Cys Gly Gly
365 370 375
Lys Phe Thr Tyr Ser Ser Gly Leu Ile Gln His Gln Arg Ile His
380 385 390
Thr Gly Glu Asn Pro Tyr Glu Cys Ser Glu Cys Gly Lys Ala Phe
395 400 405
Arg Tyr Ser Ser Ala Leu Val Arg His Gln Arg Ile His Thr Gly
410 415 420
Glu Lys Pro Leu Asn Gly Ile Gly Met Ser Lys Ser Ser Leu Arg

```
                425                 430                 435
Val Thr Thr Glu Leu Asn Ile Arg Glu Ser Thr
                440                 445
```

<210> 11
<211> 428
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID NO.: 1443262CD1

<400> 11

```
Met Glu Pro Leu Lys Val Glu Lys Phe Ala Thr Ala Asn Arg Gly
  1               5                  10                  15
Asn Gly Leu Arg Ala Val Thr Pro Leu Arg Pro Gly Glu Leu Leu
                20                  25                  30
Phe Arg Ser Asp Pro Leu Ala Tyr Thr Val Cys Lys Gly Ser Arg
                35                  40                  45
Gly Val Val Cys Asp Arg Cys Leu Leu Gly Lys Glu Lys Leu Met
                50                  55                  60
Arg Cys Ser Gln Cys Arg Val Ala Lys Tyr Cys Ser Ala Lys Cys
                65                  70                  75
Gln Lys Lys Ala Trp Pro Asp His Lys Arg Glu Cys Lys Cys Leu
                80                  85                  90
Lys Ser Cys Lys Pro Arg Tyr Pro Pro Asp Ser Val Arg Leu Leu
                95                 100                 105
Gly Arg Val Val Phe Lys Leu Met Asp Gly Ala Pro Ser Glu Ser
               110                 115                 120
Glu Lys Leu Tyr Ser Phe Tyr Asp Leu Glu Ser Asn Ile Asn Lys
               125                 130                 135
Leu Thr Glu Asp Lys Lys Glu Gly Leu Arg Gln Leu Val Met Thr
               140                 145                 150
Phe Gln His Phe Met Arg Glu Glu Ile Gln Asp Ala Ser Gln Leu
               155                 160                 165
Pro Pro Ala Phe Asp Leu Phe Glu Ala Phe Ala Lys Val Ile Cys
               170                 175                 180
Asn Ser Phe Thr Ile Cys Asn Ala Glu Met Gln Glu Val Gly Val
               185                 190                 195
Gly Leu Tyr Pro Ser Ile Ser Leu Leu Asn His Ser Cys Asp Pro
               200                 205                 210
Asn Cys Ser Ile Val Phe Asn Gly Pro His Leu Leu Leu Arg Ala
               215                 220                 225
Val Arg Asp Ile Glu Val Gly Glu Glu Leu Thr Ile Cys Tyr Leu
               230                 235                 240
Asp Met Leu Met Thr Ser Glu Glu Arg Arg Lys Gln Leu Arg Asp
               245                 250                 255
Gln Tyr Cys Phe Glu Cys Asp Cys Phe Arg Cys Gln Thr Gln Asp
               260                 265                 270
Lys Asp Ala Asp Met Leu Thr Gly Asp Glu Gln Val Trp Lys Glu
               275                 280                 285
Val Gln Glu Ser Leu Lys Lys Ile Glu Glu Leu Lys Ala His Trp
               290                 295                 300
Lys Trp Glu Gln Val Leu Ala Met Cys Gln Ala Ile Ile Ser Ser
               305                 310                 315
Asn Ser Glu Arg Leu Pro Asp Ile Asn Ile Tyr Gln Leu Lys Val
               320                 325                 330
```

```
Leu Asp Cys Ala Met Asp Ala Cys Ile Asn Leu Gly Leu Leu Glu
                335                 340                 345
Glu Ala Leu Phe Tyr Gly Thr Arg Thr Met Glu Pro Tyr Arg Ile
                350                 355                 360
Phe Phe Pro Gly Ser His Pro Val Arg Gly Val Gln Val Met Lys
                365                 370                 375
Val Gly Lys Leu Gln Leu His Gln Gly Met Phe Pro Gln Ala Met
                380                 385                 390
Lys Asn Leu Arg Leu Ala Phe Asp Ile Met Arg Val Thr His Gly
                395                 400                 405
Arg Glu His Ser Leu Ile Glu Asp Leu Ile Leu Leu Leu Glu Glu
                410                 415                 420
Cys Asp Ala Asn Ile Arg Ala Ser
                425
```

<210> 12
<211> 590
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1521648CD1

<400> 12

```
Met Ala Glu Asp Trp Leu Asp Cys Pro Ala Leu Gly Pro Gly Trp
  1               5                  10                  15
Lys Arg Arg Glu Val Phe Arg Lys Ser Gly Ala Thr Cys Gly Arg
                20                  25                  30
Ser Asp Thr Tyr Tyr Gln Ser Pro Thr Gly Asp Arg Ile Arg Ser
                35                  40                  45
Lys Val Glu Leu Thr Arg Tyr Leu Gly Pro Ala Cys Asp Leu Thr
                50                  55                  60
Leu Phe Asp Phe Lys Gln Gly Ile Leu Cys Tyr Pro Ala Pro Lys
                65                  70                  75
Ala His Pro Val Ala Val Ala Ser Lys Lys Arg Lys Lys Pro Ser
                80                  85                  90
Arg Pro Ala Lys Thr Arg Lys Arg Gln Val Gly Pro Gln Ser Gly
                95                 100                 105
Glu Val Arg Lys Glu Ala Pro Arg Asp Glu Thr Lys Ala Asp Thr
               110                 115                 120
Asp Thr Ala Pro Ala Ser Phe Pro Ala Pro Gly Cys Cys Glu Asn
               125                 130                 135
Cys Gly Ile Ser Phe Ser Gly Asp Gly Thr Gln Arg Gln Arg Leu
               140                 145                 150
Lys Thr Leu Cys Lys Asp Cys Arg Ala Gln Arg Ile Ala Phe Asn
               155                 160                 165
Arg Glu Gln Arg Met Phe Lys Arg Val Gly Cys Gly Glu Cys Ala
               170                 175                 180
Ala Cys Gln Val Thr Glu Asp Cys Gly Ala Cys Ser Thr Cys Leu
               185                 190                 195
Leu Gln Leu Pro His Asp Val Ala Ser Gly Leu Phe Cys Lys Cys
               200                 205                 210
Glu Arg Arg Arg Cys Leu Arg Ile Val Glu Arg Ser Arg Gly Cys
               215                 220                 225
Gly Val Cys Arg Gly Cys Gln Thr Gln Glu Asp Cys Gly His Cys
               230                 235                 240
Pro Ile Cys Leu Arg Pro Pro Arg Pro Gly Leu Arg Arg Gln Trp
               245                 250                 255
```

```
Lys Cys Val Gln Arg Arg Cys Leu Arg Gly Lys His Ala Arg Arg
                260                 265                 270
Lys Gly Gly Cys Asp Ser Lys Met Ala Ala Arg Arg Arg Pro Gly
                275                 280                 285
Ala Gln Pro Leu Pro Pro Pro Pro Pro Ser Gln Ser Pro Glu Pro
                290                 295                 300
Thr Glu Pro His Pro Arg Ala Leu Ala Pro Ser Pro Pro Ala Glu
                305                 310                 315
Phe Ile Tyr Tyr Cys Val Asp Glu Asp Glu Leu Gln Pro Tyr Thr
                320                 325                 330
Asn Arg Arg Gln Asn Arg Lys Cys Gly Ala Cys Ala Ala Cys Leu
                335                 340                 345
Arg Arg Met Asp Cys Gly Arg Cys Asp Phe Cys Cys Asp Lys Pro
                350                 355                 360
Lys Phe Gly Gly Ser Asn Gln Lys Arg Gln Lys Cys Arg Trp Arg
                365                 370                 375
Gln Cys Leu Gln Phe Ala Met Lys Arg Leu Leu Pro Ser Val Trp
                380                 385                 390
Ser Glu Ser Glu Asp Gly Ala Gly Ser Pro Pro Pro Tyr Arg Arg
                395                 400                 405

Arg Lys Arg Pro Ser Ser Ala Arg Arg His His Leu Gly Pro Thr
                410                 415                 420
Leu Lys Pro Thr Leu Ala Thr Arg Thr Ala Gln Pro Asp His Thr
                425                 430                 435
Gln Ala Pro Thr Lys Gln Glu Ala Gly Gly Gly Phe Val Leu Pro
                440                 445                 450
Pro Pro Gly Thr Asp Leu Val Phe Leu Arg Glu Gly Ala Ser Ser
                455                 460                 465
Pro Val Gln Val Pro Gly Pro Val Ala Ala Ser Thr Glu Ala Leu
                470                 475                 480
Leu Gln Val Lys Gln Glu Lys Ala Asp Thr Gln Asp Glu Trp Thr
                485                 490                 495
Pro Gly Thr Ala Val Leu Thr Ser Pro Val Leu Val Pro Gly Cys
                500                 505                 510
Pro Ser Lys Ala Val Asp Pro Gly Leu Pro Ser Val Lys Gln Glu
                515                 520                 525
Pro Pro Asp Pro Glu Glu Asp Lys Glu Glu Asn Lys Asp Asp Ser
                530                 535                 540
Ala Ser Lys Leu Ala Pro Glu Glu Glu Ala Gly Gly Ala Gly Thr
                545                 550                 555
Pro Val Ile Thr Glu Ile Phe Ser Leu Gly Gly Thr Arg Phe Arg
                560                 565                 570
Asp Thr Ala Val Trp Leu Pro Arg Ser Lys Asp Leu Lys Lys Pro
                575                 580                 585
Gly Ala Arg Lys Gln
                590
```

<210> 13
<211> 479
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1685494CD1

<400> 13
Met Ala Thr Ala Leu Val Ser Ala His Ser Leu Ala Pro Leu Ser

```
  1               5                  10                  15
Leu Lys Lys Glu Gly Leu Arg Val Val Arg Glu Asp His Tyr Ser
            20                  25                  30
Thr Trp Glu Gln Gly Phe Lys Leu Gln Gly Asn Ser Lys Gly Leu
            35                  40                  45
Gly Gln Glu Pro Leu Cys Lys Gln Phe Arg Gln Leu Arg Tyr Glu
            50                  55                  60
Glu Thr Thr Gly Pro Arg Glu Ala Leu Ser Arg Leu Arg Glu Leu
            65                  70                  75
Cys Gln Gln Trp Leu Gln Pro Glu Thr His Thr Lys Glu Gln Ile
            80                  85                  90
Leu Glu Leu Leu Val Leu Glu Gln Phe Leu Ile Ile Leu Pro Lys
            95                 100                 105
Glu Leu Gln Ala Arg Val Gln Glu His His Pro Glu Ser Arg Glu
           110                 115                 120
Asp Val Val Val Val Leu Glu Asp Leu Gln Leu Asp Leu Gly Glu
           125                 130                 135
Thr Gly Gln Gln Val Asp Pro Asp Gln Pro Lys Lys Gln Lys Ile
           140                 145                 150
Leu Val Glu Glu Met Ala Pro Leu Lys Gly Val Gln Glu Gln Gln
           155                 160                 165
Val Arg His Glu Cys Glu Val Thr Lys Pro Glu Lys Glu Lys Gly
           170                 175                 180
Glu Glu Thr Arg Ile Glu Asn Gly Lys Leu Ile Val Val Thr Asp
           185                 190                 195
Ser Cys Gly Arg Val Glu Ser Ser Gly Lys Ile Ser Glu Pro Met
           200                 205                 210
Glu Ala His Asn Glu Gly Ser Asn Leu Glu Arg His Gln Ala Lys
           215                 220                 225
Pro Lys Glu Lys Ile Glu Tyr Lys Cys Ser Glu Arg Glu Gln Arg
           230                 235                 240
Phe Ile Gln His Leu Asp Leu Ile Glu His Ala Ser Thr His Thr
           245                 250                 255
Gly Lys Lys Leu Cys Glu Ser Asp Val Cys Gln Ser Ser Ser Leu
           260                 265                 270
Thr Gly His Lys Lys Val Leu Ser Arg Glu Lys Gly His Gln Cys
           275                 280                 285
His Glu Cys Gly Lys Ala Phe Gln Arg Ser Ser His Leu Val Arg
           290                 295                 300
His Gln Lys Ile His Leu Gly Glu Lys Pro Tyr Gln Cys Asn Glu
           305                 310                 315
Cys Gly Lys Val Phe Ser Gln Asn Ala Gly Leu Leu Glu His Leu
           320                 325                 330
Arg Ile His Thr Gly Glu Lys Pro Tyr Leu Cys Ile His Cys Gly
           335                 340                 345
Lys Asn Phe Arg Arg Ser Ser His Leu Asn Arg His Gln Arg Ile
           350                 355                 360
His Ser Gln Glu Glu Pro Cys Glu Cys Lys Glu Cys Gly Lys Thr
           365                 370                 375
Phe Ser Gln Ala Leu Leu Leu Thr His His Gln Arg Ile His Ser
           380                 385                 390
His Ser Lys Ser His Gln Cys Asn Glu Cys Gly Lys Ala Phe Ser
           395                 400                 405
Leu Thr Ser Asp Leu Ile Arg His His Arg Ile His Thr Gly Glu
           410                 415                 420
Lys Pro Phe Lys Cys Asn Ile Cys Gln Lys Ala Phe Arg Leu Asn
           425                 430                 435
Ser His Leu Ala Gln His Val Arg Ile His Asn Glu Glu Lys Pro
           440                 445                 450
Tyr Gln Cys Ser Glu Cys Gly Glu Ala Phe Arg Gln Arg Ser Gly
           455                 460                 465
Leu Phe Gln His Gln Arg Tyr His His Lys Asp Lys Leu Ala
```

470 475

<210> 14
<211> 433
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1730829CD1

<400> 14
Met Glu Ala Val Tyr Leu Val Val Asn Gly Leu Gly Leu Val Leu
1 5 10 15
Asp Val Leu Thr Leu Val Leu Asp Leu Asn Phe Leu Leu Val Ser
20 25 30
Ser Leu Leu Ala Ser Leu Ala Trp Leu Leu Ala Phe Val Tyr Asn
35 40 45
Leu Pro His Thr Val Leu Thr Ser Leu Leu His Leu Gly Arg Gly
50 55 60
Val Leu Leu Ser Leu Leu Ala Leu Ile Glu Ala Val Val Arg Phe
65 70 75
Thr Cys Gly Gly Leu Gln Ala Leu Cys Thr Leu Leu Tyr Ser Cys
80 85 90
Cys Ser Gly Leu Glu Ser Leu Lys Leu Leu Gly His Leu Ala Ser
95 100 105
His Gly Ala Leu Arg Ser Arg Glu Ile Leu His Arg Gly Val Leu
110 115 120
Asn Val Val Ser Ser Gly His Ala Leu Leu Arg Gln Ala Cys Asp
125 130 135
Ile Cys Ala Ile Ala Met Ser Leu Val Ala Tyr Val Ile Asn Ser
140 145 150
Leu Val Asn Ile Cys Leu Ile Gly Thr Gln Asn Leu Phe Ser Leu
155 160 165
Val Leu Ala Leu Trp Asp Ala Val Thr Gly Pro Leu Trp Arg Met
170 175 180
Thr Asp Val Val Ala Ala Phe Leu Ala His Ile Ser Ser Ser Ala
185 190 195
Val Ala Met Ala Ile Leu Leu Trp Thr Pro Cys Gln Leu Ala Leu
200 205 210
Glu Leu Leu Ala Ser Ala Ala Arg Leu Leu Ala Ser Phe Val Leu
215 220 225
Val Asn Leu Thr Gly Leu Val Leu Leu Ala Cys Val Leu Ala Val
230 235 240
Thr Val Thr Val Leu His Pro Asp Phe Thr Leu Arg Leu Ala Thr
245 250 255
Gln Ala Leu Ser Gln Leu His Ala Arg Pro Ser Tyr His Arg Leu
260 265 270
Arg Glu Asp Val Met Arg Leu Ser Arg Leu Ala Leu Gly Ser Glu
275 280 285
Ala Trp Arg Arg Val Trp Ser Arg Ser Leu Gln Leu Ala Ser Trp
290 295 300
Pro Asn Arg Gly Gly Ala Pro Gly Ala Pro Gln Gly Asp Pro Met
305 310 315
Arg Val Phe Ser Val Arg Thr Arg Arg Gln Asp Thr Leu Pro Glu
320 325 330
Ala Gly Arg Arg Ser Glu Ala Glu Glu Glu Glu Ala Arg Thr Ile
335 340 345
Arg Val Thr Pro Val Arg Gly Arg Glu Arg Leu Asn Glu Glu Glu

```
                350                 355                 360
Pro Pro Gly Gly Gln Asp Pro Trp Lys Leu Leu Lys Glu Gln Glu
                365                 370                 375
Glu Arg Lys Lys Cys Val Ile Cys Gln Asp Gln Ser Lys Thr Val
                380                 385                 390
Leu Leu Leu Pro Cys Arg His Leu Cys Leu Cys Gln Ala Cys Thr
                395                 400                 405
Glu Ile Leu Met Arg His Pro Val Tyr His Arg Asn Cys Pro Leu
                410                 415                 420
Cys Arg Arg Gly Ile Leu Gln Thr Leu Asn Val Tyr Leu
                425                 430
```

<210> 15
<211> 320
<212> PRT
<213> Homo sapiens

<220>
<221> misc feature
<223> Incyte ID No.: 1864641CD1

<400> 15

```
Met Pro Lys Lys Lys Thr Gly Ala Arg Lys Lys Ala Glu Asn Arg
  1                 5                  10                  15
Arg Glu Arg Glu Lys Gln Leu Arg Ala Ser Arg Ser Thr Ile Asp
                 20                  25                  30
Leu Ala Lys His Pro Cys Asn Ala Ser Met Glu Cys Asp Lys Cys
                 35                  40                  45
Gln Arg Arg Gln Lys Asn Arg Ala Phe Cys Tyr Phe Cys Asn Ser
                 50                  55                  60
Val Gln Lys Leu Pro Ile Cys Ala Gln Cys Gly Lys Thr Lys Cys
                 65                  70                  75
Met Met Lys Ser Ser Asp Cys Val Ile Lys His Ala Gly Val Tyr
                 80                  85                  90
Ser Thr Gly Leu Ala Met Val Gly Ala Ile Cys Asp Phe Cys Glu
                 95                 100                 105
Ala Trp Val Cys His Gly Arg Lys Cys Leu Ser Thr His Ala Cys
                110                 115                 120
Ala Cys Pro Leu Thr Asp Ala Glu Cys Val Glu Cys Glu Arg Gly
                125                 130                 135
Val Trp Asp His Gly Gly Arg Ile Phe Ser Cys Ser Phe Cys His
                140                 145                 150
Asn Phe Leu Cys Glu Asp Asp Gln Phe Glu His Gln Ala Ser Cys
                155                 160                 165
Gln Val Leu Glu Ala Glu Thr Phe Lys Cys Val Ser Cys Asn Arg
                170                 175                 180
Leu Gly Gln His Ser Cys Leu Arg Cys Lys Ala Cys Phe Cys Asp
                185                 190                 195
Asp His Thr Arg Ser Lys Val Phe Lys Gln Glu Lys Gly Lys Gln
                200                 205                 210
Pro Pro Cys Pro Lys Cys Gly His Glu Thr Gln Glu Thr Lys Asp
                215                 220                 225
Leu Ser Met Ser Thr Arg Ser Leu Lys Phe Gly Arg Gln Thr Gly
                230                 235                 240
Gly Glu Glu Gly Asp Gly Ala Ser Gly Tyr Asp Ala Tyr Trp Lys
                245                 250                 255
Asn Leu Ser Ser Asp Lys Tyr Gly Asp Thr Ser Tyr His Asp Glu
                260                 265                 270
Glu Glu Asp Glu Tyr Glu Ala Glu Asp Asp Glu Glu Glu Glu Asp
```

```
                275                 280                 285
Glu Gly Arg Lys Asp Ser Asp Thr Glu Ser Ser Asp Leu Phe Thr
                290                 295                 300
Asn Leu Asn Leu Gly Arg Thr Tyr Ala Ser Gly Tyr Ala His Tyr
                305                 310                 315
Glu Glu Gln Glu Asn
                320
```

<210> 16
<211> 179
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2444604CD1

<400> 16

```
Met Ala Ala Gly Phe Phe Gln Pro Phe Met Ser Pro Arg Phe Pro
  1               5                  10                  15
Gly Gly Pro Arg Pro Thr Leu Arg Met Pro Ser Gln Pro Pro Ala
                20                  25                  30
Cys Leu Pro Gly Ser Gln Pro Leu Leu Pro Gly Ala Met Glu Pro
                35                  40                  45
Ser Pro Arg Ala Gln Gly His Pro Ser Met Gly Gly Pro Met Gln
                50                  55                  60
Arg Val Thr Pro Pro Arg Gly Met Ala Ser Val Gly Pro Gln Ser
                65                  70                  75
Tyr Gly Gly Gly Met Arg Pro Pro Pro Asn Ser Leu Ala Gly Pro
                80                  85                  90
Gly Leu Pro Ala Met Asn Met Gly Pro Gly Val Arg Gly Pro Trp
                95                 100                 105
Ala Ser Pro Ser Gly Asn Ser Ile Pro Tyr Ser Ser Ser Ser Pro
               110                 115                 120
Gly Ser Tyr Thr Gly Pro Pro Gly Gly Gly Gly Pro Pro Gly Thr
               125                 130                 135
Pro Ile Met Pro Ser Pro Gly Asp Ser Thr Asn Ser Ser Glu Asn
               140                 145                 150
Met Tyr Thr Ile Met Asn Pro Ile Gly Gln Gly Ala Gly Arg Ala
               155                 160                 165
Asn Phe Pro Leu Gly Pro Gly Pro Glu Gly Pro Trp Pro Pro
               170                 175
```

<210> 17
<211> 494
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2445008CD1

<400> 17

```
Met Gly Arg Lys Lys Lys Lys Gln Leu Lys Pro Trp Cys Trp Tyr
  1               5                  10                  15
Cys Asn Arg Asp Phe Asp Asp Glu Lys Ile Leu Ile Gln His Gln
```

```
                  20                  25                  30
Lys Ala Lys His Phe Lys Cys His Ile Cys His Lys Lys Leu Tyr
                  35                  40                  45
Thr Gly Pro Gly Leu Ala Ile His Cys Met Gln Val His Lys Glu
                  50                  55                  60
Thr Ile Asp Ala Val Pro Asn Ala Ile Pro Gly Arg Thr Asp Ile
                  65                  70                  75
Glu Leu Glu Ile Tyr Gly Met Glu Gly Ile Pro Glu Lys Asp Met
                  80                  85                  90
Asp Glu Arg Arg Arg Leu Leu Glu Gln Lys Thr Gln Glu Ser Gln
                  95                 100                 105
Lys Lys Lys Gln Gln Asp Asp Ser Asp Glu Tyr Asp Asp Asp Asp
                 110                 115                 120
Ser Ala Ala Ser Thr Ser Phe Gln Pro Gln Pro Val Gln Pro Gln
                 125                 130                 135
Gln Gly Tyr Ile Pro Pro Met Ala Gln Pro Gly Leu Pro Pro Val
                 140                 145                 150
Pro Gly Ala Pro Gly Met Pro Pro Gly Ile Pro Pro Leu Met Pro
                 155                 160                 165
Gly Val Pro Pro Leu Met Pro Gly Met Pro Pro Val Met Pro Gly
                 170                 175                 180
Met Pro Pro Gly Leu His His Gln Arg Lys Tyr Thr Gln Ser Phe
                 185                 190                 195
Cys Gly Glu Asn Ile Met Met Pro Met Gly Gly Met Met Pro Pro
                 200                 205                 210
Gly Pro Gly Ile Pro Pro Leu Met Pro Gly Met Pro Pro Gly Met
                 215                 220                 225
Pro Pro Pro Val Pro Arg Pro Gly Ile Pro Pro Met Thr Gln Ala
                 230                 235                 240
Gln Ala Val Ser Ala Pro Gly Ile Leu Asn Arg Pro Pro Ala Pro
                 245                 250                 255
Thr Ala Thr Val Pro Ala Pro Gln Pro Pro Val Thr Lys Pro Leu
                 260                 265                 270
Phe Pro Ser Ala Gly Gln Met Gly Thr Pro Val Thr Ser Ser Ser
                 275                 280                 285
Thr Ala Ser Ser Asn Ser Glu Ser Leu Ser Ala Ser Ser Lys Ala
                 290                 295                 300
Leu Phe Pro Ser Thr Ala Gln Ala Gln Ala Ala Val Gln Gly Pro
                 305                 310                 315
Val Gly Thr Asp Phe Lys Pro Leu Asn Ser Thr Pro Ala Thr Thr
                 320                 325                 330
Thr Glu Pro Pro Lys Pro Thr Phe Pro Ala Tyr Thr Gln Ser Thr
                 335                 340                 345
Ala Ser Thr Thr Ser Thr Thr Asn Ser Thr Ala Ala Lys Pro Ala
                 350                 355                 360
Ala Ser Ile Thr Ser Lys Pro Ala Thr Leu Thr Thr Thr Ser Ala
                 365                 370                 375
Thr Ser Lys Leu Ile His Pro Asp Glu Asp Ile Ser Leu Glu Glu
                 380                 385                 390
Arg Arg Ala Gln Leu Pro Lys Tyr Gln Arg Asn Leu Pro Arg Pro
                 395                 400                 405

Gly Gln Ala Pro Ile Gly Asn Pro Pro Val Gly Pro Ile Gly Gly
                 410                 415                 420
Met Met Pro Pro Gln Pro Gly Ile Pro Gln Gln Gln Gly Met Arg
                 425                 430                 435
Pro Pro Met Pro Pro His Gly Gln Tyr Gly Gly His His Gln Gly
                 440                 445                 450
Met Pro Gly Tyr Leu Pro Gly Ala Met Pro Pro Tyr Gly Gln Gly
                 455                 460                 465
Pro Pro Met Val Pro Pro Tyr Gln Gly Gly Pro Pro Arg Pro Pro
                 470                 475                 480
```

```
Met Gly Met Arg Pro Pro Val Met Ser Gln Gly Gly Arg Tyr
                485                 490
```

<210> 18
<211> 401
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2572462CD1

<400> 18

```
Met Ala Ser Ser Pro Arg Pro Lys Met Asp Ala Ile Leu Thr Glu
  1               5                  10                  15
Ala Ile Lys Ala Cys Phe Gln Lys Ser Gly Ala Ser Val Val Ala
             20                  25                  30
Ile Arg Lys Tyr Ile Ile His Lys Tyr Pro Ser Leu Glu Leu Glu
             35                  40                  45
Arg Arg Gly Tyr Leu Leu Lys Gln Ala Leu Lys Arg Glu Leu Asn
             50                  55                  60
Arg Gly Val Ile Lys Gln Val Lys Gly Lys Gly Ala Ser Gly Ser
             65                  70                  75
Phe Val Val Val Gln Lys Ser Arg Lys Thr Pro Gln Lys Ser Arg
             80                  85                  90
Asn Arg Lys Asn Arg Ser Ser Ala Val Asp Pro Glu Pro Gln Val
             95                  100                 105
Lys Leu Glu Asp Val Leu Pro Leu Ala Phe Thr Arg Leu Cys Glu
            110                 115                 120
Pro Lys Glu Ala Ser Tyr Ser Leu Ile Arg Lys Tyr Val Ser Gln
            125                 130                 135
Tyr Tyr Pro Lys Leu Arg Val Asp Ile Arg Pro Gln Leu Leu Lys
            140                 145                 150
Asn Ala Leu Gln Arg Ala Val Glu Arg Gly Gln Leu Glu Gln Ile
            155                 160                 165
Thr Gly Lys Gly Ala Ser Gly Thr Phe Gln Leu Lys Lys Ser Gly
            170                 175                 180
Glu Lys Pro Leu Leu Gly Gly Ser Leu Met Glu Tyr Ala Ile Leu
            185                 190                 195
Ser Ala Ile Ala Ala Met Asn Glu Pro Lys Thr Cys Ser Thr Thr
            200                 205                 210
Ala Leu Lys Lys Tyr Val Leu Glu Asn His Pro Gly Thr Asn Ser
            215                 220                 225
Asn Tyr Gln Met His Leu Leu Lys Lys Thr Leu Gln Lys Cys Glu
            230                 235                 240
Lys Asn Gly Trp Met Glu Gln Ile Ser Gly Lys Gly Phe Ser Gly
            245                 250                 255
Thr Phe Gln Leu Cys Phe Pro Tyr Tyr Pro Ser Pro Gly Val Leu
            260                 265                 270
Phe Pro Lys Lys Glu Pro Asp Asp Ser Arg Asp Glu Asp Glu Asp
            275                 280                 285
Glu Asp Glu Ser Ser Glu Glu Asp Ser Glu Asp Glu Glu Pro Pro
            290                 295                 300
Pro Lys Arg Arg Leu Gln Lys Lys Thr Pro Ala Lys Ser Pro Gly
            305                 310                 315
Lys Ala Ala Ser Val Lys Gln Arg Gly Ser Lys Pro Ala Pro Lys
            320                 325                 330
Val Ser Ala Ala Gln Arg Gly Lys Ala Arg Pro Leu Pro Lys Lys
            335                 340                 345
```

```
Ala Pro Pro Lys Ala Lys Thr Pro Ala Lys Lys Thr Arg Pro Ser
                350                 355                 360
Ser Thr Val Ile Lys Lys Pro Ser Gly Gly Ser Ser Lys Lys Pro
                365                 370                 375
Ala Thr Ser Ala Arg Lys Glu Val Lys Leu Pro Gly Lys Gly Lys
                380                 385                 390
Ser Thr Met Lys Lys Ser Phe Arg Val Lys Lys
                395                 400
```

<210> 19
<211> 264
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2572892CD1

<400> 19

```
Met Pro Arg Ser Phe Leu Val Arg Lys Pro Ser Asp Pro Asn Arg
  1               5                  10                  15
Lys Pro Asn Tyr Ser Glu Leu Gln Asp Ser Asn Pro Glu Phe Thr
                20                  25                  30
Phe Gln Gln Pro Tyr Asp Gln Ala His Leu Leu Ala Ala Ile Pro
                35                  40                  45
Pro Pro Glu Ile Leu Asn Pro Thr Ala Ser Leu Pro Met Leu Ile
                50                  55                  60
Trp Asp Ser Val Leu Ala Pro Gln Ala Gln Pro Ile Ala Trp Ala
                65                  70                  75
Ser Leu Arg Leu Gln Glu Ser Pro Arg Val Ala Glu Leu Thr Ser
                80                  85                  90
Leu Ser Asp Glu Asp Ser Gly Lys Gly Ser Gln Pro Pro Ser Pro
                95                 100                 105
Pro Ser Pro Ala Pro Ser Ser Phe Ser Ser Thr Ser Ala Ser Ser
               110                 115                 120
Leu Glu Ala Glu Ala Tyr Ala Ala Phe Pro Gly Leu Gly Gln Val
               125                 130                 135
Pro Lys Gln Leu Ala Gln Leu Ser Glu Ala Lys Asp Leu Gln Ala
               140                 145                 150
Arg Lys Ala Phe Asn Cys Lys Tyr Cys Asn Lys Glu Tyr Leu Ser
               155                 160                 165
Leu Gly Ala Leu Lys Met His Ile Arg Ser His Thr Leu Pro Cys
               170                 175                 180
Val Cys Gly Thr Cys Gly Lys Ala Phe Ser Arg Pro Trp Leu Leu
               185                 190                 195
Gln Gly His Val Arg Thr His Thr Gly Glu Lys Pro Phe Ser Cys
               200                 205                 210
Pro His Cys Ser Arg Ala Phe Ala Asp Arg Ser Asn Leu Arg Ala
               215                 220                 225
His Leu Gln Thr His Ser Asp Val Lys Lys Tyr Gln Cys Gln Ala
               230                 235                 240
Cys Ala Arg Thr Phe Ser Arg Met Ser Leu Leu His Lys His Gln
               245                 250                 255
Glu Ser Gly Cys Ser Gly Cys Pro Arg
               260
```

<210> 20
<211> 153
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2785674CD1

<400> 20
Met Thr Lys Ile Lys Ala Asp Pro Asp Gly Pro Glu Ala Gln Ala
1 5 10 15
Glu Ala Cys Ser Gly Glu Arg Thr Tyr Gln Glu Leu Leu Val Asn
20 25 30
Gln Asn Pro Ile Ala Gln Pro Leu Ala Ser Arg Arg Leu Thr Arg
35 40 45
Lys Leu Tyr Lys Cys Ile Lys Lys Ala Val Lys Gln Lys Gln Ile
50 55 60
Arg Arg Gly Val Lys Glu Val Gln Lys Phe Val Asn Lys Gly Glu
65 70 75
Lys Gly Ile Met Val Leu Ala Gly Asp Thr Leu Pro Ile Glu Val
80 85 90
Tyr Cys His Leu Pro Val Met Cys Glu Asp Arg Asn Leu Pro Tyr
95 100 105
Val Tyr Ile Pro Ser Lys Thr Asp Leu Gly Ala Ala Ala Gly Ser
110 115 120
Lys Arg Pro Thr Cys Val Ile Met Val Lys Pro His Glu Glu Tyr
125 130 135
Gln Glu Ala Tyr Asp Glu Cys Leu Glu Glu Val Gln Ser Leu Pro
140 145 150
Leu Pro Leu

<210> 21
<211> 243
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2797479CD1

<400> 21
Met Gly Asp Asp Ile Ser Thr His Ile Ala Pro Lys Glu Leu Arg
1 5 10 15
His Lys His Pro Ser Ser Val Asp Glu Val Ala Gln Val Val Lys
20 25 30
Gln Leu Arg Ile Ile Leu Gln Gln Gln Val Arg Pro Gly Glu Ser
35 40 45
Thr Val Leu Ala Leu Arg Pro Asn Val Gln Gln Ile Glu Ala Pro
50 55 60
Asp Val Ser Arg Asp Pro Arg Val Leu Gly Phe Asp Phe Pro Gly
65 70 75
Ser Ala Arg Ile His Glu Gly Thr His Thr Leu Glu Lys Pro Tyr
80 85 90
Glu Cys Lys Gln Cys Gly Lys Leu Leu Ser His Arg Ser Ser Phe
95 100 105
Arg Arg His Met Met Ala His Thr Gly Asp Gly Pro His Lys Cys
110 115 120
Thr Val Cys Gly Lys Ala Phe Asp Ser Pro Ser Val Phe Gln Arg

```
                125                 130                 135
His Glu Arg Thr His Thr Gly Glu Lys Pro Tyr Glu Cys Lys Gln
                140                 145                 150
Cys Gly Lys Ala Phe Arg Thr Ser Ser Ser Leu Arg Lys His Glu
                155                 160                 165
Thr Thr His Thr Gly Glu Gln Pro Tyr Lys Cys Lys Cys Gly Lys
                170                 175                 180

Ala Phe Ser Asp Leu Phe Ser Phe Gln Ser His Glu Thr Thr His
                185                 190                 195
Ser Glu Glu Glu Pro Tyr Glu Cys Lys Glu Cys Gly Lys Ala Phe
                200                 205                 210
Ser Ser Phe Lys Tyr Phe Cys Arg His Glu Arg Thr His Ser Glu
                215                 220                 225
Glu Lys Ser Tyr Glu Cys Gln Ile Cys Gly Lys Leu Ser Val Val
                230                 235                 240
Ser Val Thr
```

<210> 22
<211> 485
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2960640CD1

<400> 22

```
Met Arg Asp Asn Arg Ala Val Ser Leu Cys Gln Gln Glu Trp Met
  1                 5                  10                  15
Cys Pro Gly Pro Ala Gln Arg Ala Leu Tyr Arg Gly Ala Thr Gln
                 20                  25                  30
Arg Lys Asp Ser His Val Ser Leu Ala Thr Gly Val Pro Trp Gly
                 35                  40                  45
Tyr Glu Glu Thr Lys Thr Leu Leu Ala Ile Leu Ser Ser Ser Gln
                 50                  55                  60
Phe Tyr Gly Lys Leu Gln Thr Cys Gln Gln Asn Ser Gln Ile Tyr
                 65                  70                  75
Arg Ala Met Ala Glu Gly Leu Trp Glu Gln Gly Phe Leu Arg Thr
                 80                  85                  90
Pro Glu Gln Cys Arg Thr Lys Phe Lys Ser Leu Gln Leu Ser Tyr
                 95                 100                 105
Arg Lys Val Arg Arg Gly Arg Val Pro Glu Pro Cys Ile Phe Tyr
                110                 115                 120
Glu Glu Met Asn Ala Leu Ser Gly Ser Trp Ala Ser Ala Pro Pro
                125                 130                 135
Met Ala Ser Asp Ala Val Pro Gly Gln Glu Gly Ser Asp Ile Glu
                140                 145                 150
Ala Gly Glu Leu Asn His Gln Asn Gly Glu Pro Thr Glu Val Glu
                155                 160                 165
Asp Gly Thr Val Asp Gly Ala Asp Arg Asp Glu Lys Asp Phe Arg
                170                 175                 180
Asn Pro Gly Gln Glu Val Arg Lys Leu Asp Leu Pro Val Leu Phe
                185                 190                 195
Pro Asn Arg Leu Gly Phe Glu Phe Lys Asn Glu Ile Lys Lys Glu
                200                 205                 210
Asn Leu Lys Trp Asp Asp Ser Glu Glu Val Glu Ile Asn Lys Ala
                215                 220                 225
Leu Gln Arg Lys Ser Arg Gly Val Tyr Trp His Ser Glu Leu Gln
```

```
                230                 235                 240
Lys Gly Leu Glu Ser Glu Pro Thr Ser Arg Arg Gln Cys Arg Asn
                245                 250                 255
Ser Pro Gly Glu Ser Glu Glu Lys Thr Pro Ser Gln Glu Lys Met
                260                 265                 270
Ser His Gln Ser Phe Cys Ala Arg Asp Lys Ala Cys Thr His Ile
                275                 280                 285
Leu Cys Gly Lys Asn Cys Ser Gln Ser Val His Ser Pro His Lys
                290                 295                 300
Pro Ala Leu Lys Leu Glu Lys Val Ser Gln Cys Pro Glu Cys Gly
                305                 310                 315
Lys Thr Phe Ser Arg Ser Ser Tyr Leu Val Arg His Gln Arg Ile
                320                 325                 330

His Thr Gly Glu Lys Pro His Lys Cys Ser Glu Cys Gly Lys Gly
                335                 340                 345
Phe Ser Glu Arg Ser Asn Leu Thr Ala His Leu Arg Thr His Thr
                350                 355                 360
Gly Glu Arg Pro Tyr Gln Cys Gly Gln Cys Gly Lys Ser Phe Asn
                365                 370                 375
Gln Ser Ser Ser Leu Ile Val His Gln Arg Thr His Thr Gly Glu
                380                 385                 390
Lys Pro Tyr Gln Cys Ile Val Cys Gly Lys Arg Phe Asn Asn Ser
                395                 400                 405
Ser Gln Phe Ser Ala His Arg Arg Ile His Thr Gly Glu Ser Pro
                410                 415                 420
Tyr Lys Cys Ala Val Cys Gly Lys Ile Phe Asn Asn Ser Ser His
                425                 430                 435
Phe Ser Ala His Arg Lys Thr His Thr Gly Glu Lys Pro Tyr Arg
                440                 445                 450
Cys Ser His Cys Glu Arg Gly Phe Thr Lys Asn Ser Ala Leu Thr
                455                 460                 465
Arg His Gln Thr Val His Met Lys Ala Val Leu Ser Ser Gln Glu
                470                 475                 480
Gly Arg Asp Ala Leu
                485
```

<210> 23
<211> 160
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3454051CD1

```
<400> 23
Met Ser Trp Thr Cys Pro Arg Cys Gln Gln Pro Val Phe Phe Ala
  1               5                  10                  15
Glu Lys Val Ser Ser Leu Gly Lys Asn Trp His Arg Phe Cys Leu
                20                  25                  30
Lys Cys Glu Arg Cys His Ser Ile Leu Ser Pro Gly Gly His Ala
                35                  40                  45
Glu His Asn Gly Arg Pro Tyr Cys His Lys Pro Cys Tyr Gly Ala
                50                  55                  60
Leu Phe Gly Pro Arg Gly Pro Pro His Met Lys Thr Phe Thr Gly
                65                  70                  75
Glu Thr Ser Leu Cys Pro Gly Cys Gly Glu Pro Val Tyr Phe Ala
                80                  85                  90
```

```
Glu Lys Val Met Ser Leu Gly Arg Asn Trp His Arg Pro Cys Leu
                95                  100                 105
Arg Cys Gln Arg Cys His Lys Thr Leu Thr Ala Gly Ser His Ala
            110                 115                 120
Glu His Asp Gly Val Pro Tyr Cys His Val Pro Cys Tyr Gly Tyr
            125                 130                 135
Leu Phe Gly Pro Lys Gly Val Asn Ile Gly Asp Val Gly Cys Tyr
            140                 145                 150
Ile Tyr Asp Pro Val Lys Ile Lys Phe Lys
            155                 160
```

<210> 24
<211> 511
<212> PRT
<213> Homo sapiens

<220>
<221>
<223> Incyte ID No.: 3510640CD1

```
<400> 24
Met Gln Glu Leu Tyr Ser Thr Pro Ala Ser Arg Leu Asp Ser Phe
  1               5                  10                  15
Val Ala Gln Trp Leu Gln Pro His Arg Glu Trp Lys Glu Glu Val
            20                  25                  30
Leu Asp Ala Val Arg Thr Val Glu Glu Phe Leu Arg Gln Glu His
            35                  40                  45
Phe Gln Gly Lys Arg Gly Leu Asp Gln Asp Val Arg Val Leu Lys
            50                  55                  60
Val Val Lys Val Gly Ser Phe Gly Asn Gly Thr Val Leu Arg Ser
            65                  70                  75
Thr Arg Glu Val Glu Leu Val Ala Phe Leu Ser Cys Phe His Ser
            80                  85                  90
Phe Gln Glu Ala Ala Lys His His Lys Asp Val Leu Arg Leu Ile
            95                 100                 105
Trp Lys Thr Met Trp Gln Ser Gln Asp Leu Leu Asp Leu Gly Leu
            110                 115                 120
Glu Asp Leu Arg Met Glu Gln Arg Val Pro Asp Ala Leu Val Phe
            125                 130                 135
Thr Ile Gln Thr Arg Gly Thr Ala Glu Pro Ile Thr Val Thr Ile
            140                 145                 150
Val Pro Ala Tyr Arg Ala Leu Gly Pro Ser Leu Pro Asn Ser Gln
            155                 160                 165
Pro Pro Pro Glu Val Tyr Val Ser Leu Ile Lys Ala Cys Gly Gly
            170                 175                 180
Pro Gly Asn Phe Cys Pro Phe Phe Ser Glu Leu Gln Arg Asn Phe
            185                 190                 195
Val Lys His Arg Pro Thr Lys Leu Lys Ser Leu Leu Arg Leu Val
            200                 205                 210
Lys His Trp Tyr Gln Gln Tyr Val Lys Ala Arg Ser Pro Arg Ala
            215                 220                 225
Asn Leu Pro Pro Leu Tyr Ala Leu Glu Leu Leu Thr Ile Tyr Ala
            230                 235                 240
Trp Glu Met Gly Thr Glu Glu Asp Glu Asn Phe Met Leu Asp Glu
            245                 250                 255
Gly Phe Thr Thr Val Met Asp Leu Leu Leu Glu Tyr Glu Val Ile
            260                 265                 270
Cys Ile Tyr Trp Thr Lys Tyr Tyr Thr Leu His Asn Ala Ile Ile
```

```
                275                 280                 285
Glu Asp Cys Val Arg Lys Gln Leu Lys Lys Glu Arg Pro Ile Ile
                290                 295                 300
Leu Asp Pro Ala Asp Pro Thr Leu Asn Val Ala Glu Gly Tyr Arg
                305                 310                 315
Trp Asp Ile Val Ala Gln Arg Ala Ser Gln Cys Leu Lys Gln Asp
                320                 325                 330
Cys Cys Tyr Asp Asn Arg Glu Asn Pro Ile Ser Ser Trp Asn Val
                335                 340                 345
Lys Arg Ala Arg Asp Ile His Leu Thr Val Glu Gln Arg Gly Tyr
                350                 355                 360
Pro Asp Phe Asn Leu Ile Val Asn Pro Tyr Glu Pro Ile Arg Lys
                365                 370                 375
Val Lys Glu Lys Ile Arg Arg Thr Arg Gly Tyr Ser Gly Leu Gln
                380                 385                 390
Arg Leu Ser Phe Gln Val Pro Gly Ser Glu Arg Gln Leu Leu Ser
                395                 400                 405
Ser Arg Cys Ser Leu Ala Lys Tyr Gly Ile Phe Ser His Thr His
                410                 415                 420
Ile Tyr Leu Leu Glu Thr Ile Pro Ser Glu Ile Gln Val Phe Val
                425                 430                 435
Lys Asn Pro Asp Gly Gly Ser Tyr Ala Tyr Ala Ile Asn Pro Asn
                440                 445                 450
Ser Phe Ile Leu Gly Leu Lys Gln Gln Ile Glu Asp Gln Gln Gly
                455                 460                 465

Leu Pro Lys Lys Gln Gln Gln Leu Glu Phe Gln Gly Gln Val Leu
                470                 475                 480
Gln Asp Trp Leu Gly Leu Gly Ile Tyr Gly Ile Gln Asp Ser Asp
                485                 490                 495
Thr Leu Ile Leu Ser Lys Lys Lys Gly Glu Ala Leu Phe Pro Ala
                500                 505                 510
Ser
```

<210> 25
<211> 310
<212> PRT
<213> Homo sapiens

<220> -
<223> Incyte ID No.: 3815083CD1

<400> 25

```
Met Arg Pro Leu Gln Ile Val Pro Ser Arg Leu Ile Ser Gln Leu
  1                 5                  10                  15
Tyr Cys Gly Leu Lys Pro Pro Ala Ser Thr Arg Asn Gln Ile Cys
                 20                  25                  30
Leu Lys Met Ala Arg Pro Ser Ser Ser Met Ala Asp Phe Arg Lys
                 35                  40                  45
Phe Phe Ala Lys Ala Lys His Ile Val Ile Ile Ser Gly Ala Gly
                 50                  55                  60
Val Ser Ala Glu Ser Gly Val Pro Thr Phe Arg Gly Ala Gly Gly
                 65                  70                  75
Tyr Trp Arg Lys Trp Gln Ala Gln Asp Leu Ala Thr Pro Leu Ala
                 80                  85                  90
Phe Ala His Asn Pro Ser Arg Val Trp Glu Phe Tyr His Tyr Arg
                 95                 100                 105
Arg Glu Val Met Gly Ser Lys Glu Pro Asn Ala Gly His Arg Ala
                110                 115                 120
```

```
Ile Ala Glu Cys Glu Thr Arg Leu Gly Lys Gln Gly Arg Arg Val
                125                 130                 135
Val Val Ile Thr Gln Asn Ile Asp Glu Leu His Arg Lys Ala Gly
                140                 145                 150
Thr Lys Asn Leu Leu Glu Ile His Gly Ser Leu Phe Lys Thr Arg
                155                 160                 165
Cys Thr Ser Cys Gly Val Val Ala Glu Asn Tyr Lys Ser Pro Ile
                170                 175                 180
Cys Pro Ala Leu Ser Gly Lys Gly Ala Pro Glu Pro Gly Thr Gln
                185                 190                 195
Asp Ala Ser Ile Pro Val Glu Lys Leu Pro Arg Cys Glu Glu Ala
                200                 205                 210
Gly Cys Gly Gly Leu Leu Arg Pro His Val Val Trp Phe Gly Glu
                215                 220                 225
Asn Leu Asp Pro Ala Ile Leu Glu Glu Val Asp Arg Glu Leu Ala
                230                 235                 240
His Cys Asp Leu Cys Leu Val Val Gly Thr Ser Ser Val Val Tyr
                245                 250                 255
Pro Ala Ala Met Phe Ala Pro Gln Val Ala Ala Arg Gly Val Pro
                260                 265                 270
Val Ala Glu Phe Asn Thr Glu Thr Thr Pro Ala Thr Asn Arg Phe
                275                 280                 285
Arg Phe His Phe Gln Gly Pro Cys Gly Thr Thr Leu Pro Glu Ala
                290                 295                 300
Leu Ala Cys His Glu Asn Glu Thr Val Ser
                305                 310
```

<210> 26
<211> 331
<212> PRT
<213> Homo sapiens

<220> -
<221> misc-feature
<223> Incyte ID No.: 3988457CD1

<400> 26

```
Met Ala Ile Asn Arg Phe Arg Leu Glu Asn Asp Leu Glu Glu Leu
  1                 5                  10                  15
Ala Leu Tyr Gln Ile Gln Leu Leu Lys Asp Leu Arg His Thr Glu
                 20                  25                  30
Asn Glu Glu Asp Lys Val Ser Ser Ser Ser Phe Arg Gln Arg Met
                 35                  40                  45
Leu Gly Asn Leu Leu Arg Pro Pro Tyr Glu Arg Pro Glu Leu Pro
                 50                  55                  60
Thr Cys Leu Tyr Val Ile Gly Leu Thr Gly Ile Ser Gly Ser Gly
                 65                  70                  75
Lys Ser Ser Ile Ala Gln Arg Leu Lys Gly Leu Gly Ala Phe Val
                 80                  85                  90
Ile Asp Ser Asp His Leu Gly His Arg Ala Tyr Ala Pro Gly Gly
                 95                 100                 105
Pro Ala Tyr Gln Pro Val Val Glu Ala Phe Gly Thr Asp Ile Leu
                110                 115                 120
His Lys Asp Gly Ile Ile Asn Arg Lys Val Leu Gly Ser Arg Val
                125                 130                 135
Phe Gly Asn Lys Lys Gln Leu Lys Ile Leu Thr Asp Ile Met Trp
                140                 145                 150
Pro Ile Ile Ala Lys Leu Ala Arg Glu Glu Met Asp Arg Ala Val
                155                 160                 165
Ala Glu Gly Lys Arg Val Cys Val Ile Asp Ala Ala Val Leu Leu
                170                 175                 180
```

```
Glu Ala Gly Trp Gln Asn Leu Val His Glu Val Trp Thr Ala Val
                185                 190                 195
Ile Pro Glu Thr Glu Ala Val Arg Arg Ile Val Glu Arg Asp Gly
                200                 205                 210
Leu Ser Glu Ala Ala Ala Gln Ser Arg Leu Gln Ser Gln Met Ser
                215                 220                 225
Gly Gln Gln Leu Val Glu Gln Ser His Val Val Leu Ser Ser Pro
                230                 235                 240
Cys Gly Ser Arg Ile Ser Pro Asn Ala Arg Trp Arg Lys Pro Gly
                245                 250                 255
Pro Ser Cys Arg Ser Ala Phe Pro Arg Leu Ile Arg Pro Ser Thr
                260                 265                 270
Glu Lys Phe Ser Val Gly Pro Asp Trp Leu Leu Glu Leu Thr Ser
                275                 280                 285
Asp Pro Val Val Arg Arg Asn Gly Gly Leu Asp Ala His Pro Gly
                290                 295                 300
Ser Gly Pro Glu Val Gln Ala Ile Leu Cys Arg Thr Trp Pro Gly
                305                 310                 315
Leu Val Asp Thr Gly Ser Leu Pro Asn Thr Leu Val Phe Gly Gln
                320                 325                 330
His
```

<210> 27
<211> 200
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 131890CD1

<400> 27

```
Met Met Thr Ala Glu Ser Arg Glu Ala Thr Gly Leu Ser Pro Gln
  1               5                  10                  15
Ala Ala Gln Glu Lys Asp Gly Ile Val Ile Val Lys Val Glu Glu
                20                  25                  30
Glu Asp Glu Glu Asp His Met Trp Gly Gln Asp Ser Thr Leu Gln
                35                  40                  45
Asp Thr Pro Pro Pro Asp Pro Glu Ile Phe Arg Gln Arg Phe Arg
                50                  55                  60
Arg Phe Cys Tyr Gln Asn Thr Phe Gly Pro Arg Glu Ala Leu Ser
                65                  70                  75
Arg Leu Lys Glu Leu Cys His Gln Trp Leu Arg Pro Glu Ile Asn
                80                  85                  90
Thr Lys Glu Gln Ile Leu Glu Leu Leu Val Leu Glu Gln Phe Leu
                95                 100                 105
Ser Ile Leu Pro Lys Glu Leu Gln Val Trp Leu Gln Glu Tyr Arg
                110                115                 120
Pro Asp Ser Gly Glu Glu Ala Val Thr Leu Leu Glu Asp Leu Glu
                125                130                 135
Leu Asp Leu Ser Gly Gln Gln Val Pro Gly Gln Val His Gly Pro
                140                145                 150
Glu Met Leu Ala Arg Gly Met Val Pro Leu Asp Pro Val Gln Glu
                155                160                 165
Ser Ser Ser Phe Asp Leu His His Glu Ala Thr Gln Ser His Phe
                170                175                 180
Lys His Ser Ser Arg Lys Pro Arg Leu Leu Gln Ser Arg Gly Lys
                185                190                 195
Lys Gln Gly Phe Ile
```

200

<210> 28
<211> 100
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 238642CD1

<400> 28
Met Gln Lys Pro Cys Lys Glu Asn Glu Gly Lys Pro Lys Cys Ser
1 5 10 15
Val Pro Lys Arg Glu Glu Lys Arg Pro Tyr Gly Glu Phe Glu Arg
20 25 30
Gln Gln Thr Glu Gly Asn Phe Arg Gln Arg Leu Leu Gln Ser Leu
35 40 45
Glu Glu Phe Lys Glu Asp Ile Asp Tyr Arg His Phe Lys Asp Glu
50 55 60
Glu Met Thr Arg Glu Gly Asp Glu Met Glu Arg Cys Leu Glu Glu
65 70 75
Ile Arg Gly Leu Arg Lys Lys Phe Arg Ala Leu His Ser Asn His
80 85 90
Arg His Ser Arg Asp Arg Pro Tyr Pro Ile
95 100

<210> 29
<211> 528
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 669862CD1

<400> 29
Met Ser Ser Pro Tyr Pro Leu Leu Leu Glu Asn Ser Ile Cys Leu
1 5 10 15
Phe Phe His Phe Leu Pro Asp Phe Asn Phe Thr Thr Glu Ser Asn
20 25 30
Lys Leu Ser Ser Glu Lys Arg Asn Tyr Glu Val Asn Ala Tyr His
35 40 45
Gln Glu Thr Trp Lys Arg Asn Lys Thr Phe Asn Leu Met Arg Phe
50 55 60
Ile Phe Arg Thr Asp Pro Gln Tyr Thr Ile Glu Phe Gly Arg Gln
65 70 75
Gln Arg Pro Lys Val Gly Cys Phe Ser Gln Met Ile Phe Lys Lys
80 85 90
His Lys Ser Leu Pro Leu His Lys Arg Asn Asn Thr Arg Glu Lys
95 100 105
Ser Tyr Glu Cys Lys Glu Tyr Lys Lys Gly Phe Arg Lys Tyr Leu
110 115 120
His Leu Thr Glu His Leu Arg Asp His Thr Gly Val Ile Pro Tyr
125 130 135
Glu Cys Asn Glu Cys Gly Lys Ala Phe Val Val Phe Gln His Phe

```
                  140                 145                 150
Ile Arg His Arg Lys Ile His Thr Asp Leu Lys Pro Tyr Glu Cys
                  155                 160                 165
Asn Gly Cys Glu Lys Ala Phe Arg Phe Tyr Ser Gln Leu Ile Gln
                  170                 175                 180
His Gln Ile Ile His Thr Gly Met Lys Pro Tyr Glu Cys Lys Gln
                  185                 190                 195
Cys Gly Lys Ala Phe Arg Arg His Ser His Leu Thr Glu His Gln
                  200                 205                 210
Lys Ile His Val Gly Leu Lys Pro Phe Glu Cys Lys Glu Cys Gly
                  215                 220                 225
Glu Thr Phe Arg Leu Tyr Arg His Met Cys Leu His Gln Lys Ile
                  230                 235                 240
His His Gly Val Lys Pro Tyr Lys Cys Lys Glu Cys Gly Lys Ala
                  245                 250                 255
Phe Gly His Arg Ser Ser Leu Tyr Gln His Lys Lys Ile His Ser
                  260                 265                 270
Gly Glu Lys Pro Tyr Lys Cys Glu Gln Cys Glu Lys Ala Phe Val
                  275                 280                 285
Arg Ser Tyr Leu Leu Val Glu His Gln Arg Ser His Thr Gly Glu
                  290                 295                 300
Lys Pro His Glu Cys Met Glu Cys Gly Lys Ala Phe Ser Lys Gly
                  305                 310                 315
Ser Ser Leu Leu Lys His Lys Arg Ile His Ser Ser Glu Lys Leu
                  320                 325                 330
Tyr Asp Cys Lys Asp Cys Gly Lys Ala Phe Cys Arg Gly Ser Gln
                  335                 340                 345
Leu Thr Gln His Gln Arg Ile His Thr Gly Glu Lys Pro His Glu
                  350                 355                 360
Cys Lys Glu Cys Gly Lys Thr Phe Lys Leu His Ser Tyr Leu Ile
                  365                 370                 375
Gln His Gln Ile Ile His Thr Asp Leu Lys Pro Tyr Glu Cys Lys
                  380                 385                 390
Gln Cys Gly Lys Ala Phe Ser Arg Val Gly Asp Leu Lys Thr His
                  395                 400                 405
Gln Ser Ile His Ala Gly Glu Lys Pro Tyr Glu Cys Lys Glu Cys
                  410                 415                 420
Gly Lys Thr Phe Arg Leu Asn Ser Gln Leu Ile Tyr His Gln Thr
                  425                 430                 435
Ile His Thr Gly Leu Lys Pro Tyr Val Cys Lys Glu Cys Lys Lys
                  440                 445                 450
Ala Phe Arg Ser Ile Ser Gly Leu Ser Gln His Lys Arg Ile His
                  455                 460                 465
Thr Gly Glu Lys Pro Tyr Glu Cys Lys Glu Cys Asp Lys Ala Phe
                  470                 475                 480
Asn Arg Ser Asp Arg Leu Thr Gln His Glu Thr Ile His Thr Gly
                  485                 490                 495
Val Lys Pro Gln Lys Cys Lys Glu Cys Gly Lys Ala Phe Ser His
                  500                 505                 510
Cys Tyr Gln Leu Ser Gln His Gln Arg Phe His His Gly Glu Arg
                  515                 520                 525
Leu Leu Met
```

<210> 30
<211> 350
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1003663CD1

<400> 30
Met His Pro Ala Ala Phe Pro Leu Pro Val Val Val Ala Ala Val
1 5 10 15
Leu Trp Gly Ala Ala Pro Thr Arg Gly Leu Ile Arg Ala Thr Ser
20 25 30
Asp His Asn Ala Ser Met Asp Phe Ala Asp Leu Pro Ala Leu Phe
35 40 45
Gly Ala Thr Leu Ser Gln Glu Gly Leu Gln Gly Phe Leu Val Glu
50 55 60
Ala His Pro Asp Asn Ala Cys Ser Pro Ile Ala Pro Pro Pro Pro
65 70 75
Ala Pro Val Asn Gly Ser Val Phe Ile Ala Leu Leu Arg Arg Phe
80 85 90
Asp Cys Asn Phe Asp Leu Lys Val Leu Asn Ala Gln Lys Ala Gly
95 100 105
Tyr Gly Ala Ala Val Val His Asn Val Asn Ser Asn Glu Leu Leu
110 115 120
Asn Met Val Trp Asn Ser Glu Glu Ile Gln Gln Gln Ile Trp Ile
125 130 135
Pro Ser Val Phe Ile Gly Glu Arg Ser Ser Glu Tyr Leu Arg Ala
140 145 150
Leu Phe Val Tyr Glu Lys Gly Ala Arg Val Leu Leu Val Pro Asp
155 160 165
Asn Thr Phe Pro Leu Gly Tyr Tyr Leu Ile Pro Phe Thr Gly Ile
170 175 180
Val Gly Leu Leu Val Leu Ala Met Gly Ala Val Met Ile Ala Arg
185 190 195
Cys Ile Gln His Arg Lys Arg Leu Gln Arg Asn Arg Leu Thr Lys
200 205 210
Glu Gln Leu Lys Gln Ile Pro Thr His Asp Tyr Gln Lys Gly Asp
215 220 225
Gln Tyr Asp Val Cys Ala Ile Cys Leu Asp Glu Tyr Glu Asp Gly
230 235 240
Asp Lys Leu Arg Val Leu Pro Cys Ala His Ala Tyr His Ser Arg
245 250 255
Cys Val Asp Pro Trp Leu Thr Gln Thr Arg Lys Thr Cys Pro Ile
260 265 270
Cys Lys Gln Pro Val His Arg Gly Pro Gly Asp Glu Asp Gln Glu
275 280 285
Glu Glu Thr Gln Gly Gln Glu Glu Gly Asp Glu Gly Glu Pro Arg
290 295 300
Asp His Pro Ala Ser Glu Arg Thr Pro Leu Leu Gly Ser Ser Pro
305 310 315
Thr Leu Pro Thr Ser Phe Gly Ser Leu Ala Pro Ala Pro Leu Val
320 325 330
Phe Pro Gly Pro Ser Thr Asp Pro Pro Leu Ser Pro Pro Ser Ser
335 340 345
Pro Val Ile Leu Val
350

<210> 31
<211> 315
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1432557CD1

<400> 31
Met Ala Ala Leu Gly Val Leu Glu Ser Asp Leu Pro Ser Ala Val
1 5 10 15
Thr Leu Leu Lys Asn Leu Gln Glu Gln Val Met Ala Val Thr Ala
20 25 30
Gln Val Lys Ser Leu Thr Gln Lys Val Gln Ala Gly Ala Tyr Pro
35 40 45
Thr Glu Lys Gly Leu Ser Phe Leu Glu Val Lys Asp Gln Leu Leu
50 55 60
Leu Met Tyr Leu Met Asp Leu Thr His Leu Ile Leu Asp Lys Ala
65 70 75
Ser Gly Gly Ser Leu Gln Gly His Asp Ala Val Leu Arg Leu Val
80 85 90
Glu Ile Arg Thr Val Leu Glu Lys Leu Arg Pro Leu Asp Gln Lys
95 100 105
Leu Lys Tyr Gln Ile Asp Lys Leu Ile Lys Thr Ala Val Thr Gly
110 115 120
Ser Leu Ser Glu Asn Asp Pro Leu Arg Phe Lys Pro His Pro Ser
125 130 135
Asn Met Met Ser Lys Leu Ser Ser Glu Asp Glu Glu Glu Asp Glu
140 145 150
Ala Glu Asp Asp Gln Ser Glu Ala Ser Gly Lys Lys Ser Val Lys
155 160 165
Gly Val Ser Lys Lys Tyr Val Pro Pro Arg Leu Val Pro Val His
170 175 180
Tyr Asp Glu Thr Glu Ala Glu Arg Glu Lys Lys Arg Leu Glu Arg
185 190 195
Ala Lys Arg Arg Ala Leu Ser Ser Ser Val Ile Arg Glu Leu Lys
200 205 210
Glu Gln Tyr Ser Asp Ala Pro Glu Glu Ile Arg Asp Ala Arg His
215 220 225
Pro His Val Thr Arg Gln Ser Gln Glu Asp Gln His Arg Ile Asn
230 235 240
Tyr Glu Glu Ser Met Met Val Arg Leu Ser Val Ser Lys Arg Glu
245 250 255
Lys Gly Arg Arg Lys Arg Ala Asn Val Met Ser Ser Gln Leu His
260 265 270
Ser Leu Thr His Phe Ser Asp Ile Ser Ala Leu Thr Gly Gly Thr
275 280 285
Val His Leu Asp Glu Asp Gln Asn Pro Ile Lys Lys Arg Lys Lys
290 295 300
Ile Pro Gln Lys Gly Arg Lys Lys Lys Gly Phe Arg Arg Arg Arg
305 310 315

<210> 32
<211> 120
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> 1441770CD1

<400> 32
Met Asp Asp Ser Lys Val Val Gly Gly Lys Val Lys Lys Pro Gly
1 5 10 15
Lys Arg Gly Arg Lys Pro Ala Lys Ile Asp Leu Lys Ala Lys Leu
20 25 30
Glu Arg Ser Arg Gln Ser Ala Arg Glu Cys Arg Ala Arg Lys Lys
35 40 45

```
Leu Arg Tyr Gln Tyr Leu Glu Glu Leu Val Ser Ser Arg Glu Arg
                50                  55                  60
Ala Ile Cys Ala Leu Arg Glu Glu Leu Glu Met Tyr Lys Gln Trp
                65                  70                  75
Cys Met Ala Met Asp Gln Gly Lys Ile Pro Ser Glu Ile Lys Ala
                80                  85                  90
Leu Leu Thr Gly Glu Glu Gln Asn Lys Ser Gln Gln Asn Ser Ser
                95                 100                 105
Arg His Thr Lys Ala Gly Lys Thr Asp Ala Asn Ser Asn Ser Trp
               110                 115                 120
```

<210> 33
<211> 326
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1456684CD1

<400> 33

```
Met Gln Glu Glu Pro Leu Pro Gln Gly Asn Asp Pro Glu Pro Ser
  1                 5                  10                  15
Gly Asp Ser Pro Leu Gly Leu Cys Gln Ser Glu Cys Met Glu Met
                20                  25                  30
Ser Glu Val Phe Asp Asp Ala Ser Asp Gln Asp Ser Thr Asp Lys
                35                  40                  45
Pro Trp Arg Pro Tyr Tyr Asn Tyr Lys Pro Lys Lys Lys Ser Arg
                50                  55                  60
Gln Leu Lys Lys Met Arg Lys Val Asn Trp Arg Lys Glu His Gly
                65                  70                  75
Asn Arg Ser Pro Ser His Lys Cys Lys Tyr Pro Ala Glu Leu Asp
                80                  85                  90
Cys Ala Val Gly Lys Ala Pro Gln Asp Lys Pro Phe Glu Glu Glu
                95                 100                 105
Glu Thr Lys Glu Met Pro Lys Leu Gln Cys Glu Leu Cys Asp Gly
               110                 115                 120
Asp Lys Ala Val Gly Ala Gly Asn Gln Gly Arg Pro His Arg His
               125                 130                 135
Leu Thr Ser Arg Pro Tyr Ala Cys Glu Leu Cys Ala Lys Gln Phe
               140                 145                 150
Gln Ser Pro Ser Thr Leu Lys Met His Met Arg Cys His Thr Gly
               155                 160                 165
Glu Lys Pro Tyr Gln Cys Lys Thr Cys Gly Arg Cys Phe Ser Val
               170                 175                 180
Gln Gly Asn Leu Gln Lys His Glu Arg Ile His Leu Gly Leu Lys
               185                 190                 195
Glu Phe Val Cys Gln Tyr Cys Asn Lys Ala Phe Thr Leu Asn Glu
               200                 205                 210
Thr Leu Lys Ile His Glu Arg Ile His Thr Gly Glu Lys Arg Tyr
               215                 220                 225
His Cys Gln Phe Cys Phe Gln Arg Phe Leu Tyr Leu Ser Thr Lys
               230                 235                 240
Arg Asn His Glu Gln Arg His Ile Arg Glu His Asn Gly Lys Gly
               245                 250                 255
Tyr Ala Cys Phe Gln Cys Pro Lys Ile Cys Lys Thr Ala Ala Ala
               260                 265                 270
Leu Gly Met His Gln Lys Lys His Leu Phe Lys Ser Pro Ser Gln
               275                 280                 285
```

```
Gln Glu Lys Ile Gly Asp Val Cys His Glu Asn Ser Asn Pro Leu
                290                 295                 300
Glu Asn Gln His Phe Ile Gly Ser Glu Asp Asn Asp Gln Lys Asp
                305                 310                 315
Asn Ile Gln Thr Gly Val Glu Asn Val Val Leu
                320                 325
```

<210> 34
<211> 106
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1602916CD1

<400> 34

```
Met Phe Pro Trp Met Arg Pro Gln Ala Ala Pro Gly Arg Arg Arg
  1                 5                  10                  15
Gly Arg Gln Thr Tyr Ser Arg Phe Gln Thr Leu Glu Leu Glu Lys
                 20                  25                  30
Glu Phe Leu Phe Asn Pro Tyr Leu Thr Arg Lys Arg Arg Ile Glu
                 35                  40                  45
Val Ser His Ala Leu Ala Leu Thr Glu Arg Gln Val Lys Ile Trp
                 50                  55                  60
Phe Gln Asn Arg Arg Met Lys Trp Lys Lys Glu Asn Asn Lys Asp
                 65                  70                  75
Lys Phe Pro Val Ser Arg Gln Glu Val Lys Asp Gly Glu Thr Lys
                 80                  85                  90
Lys Glu Ala Gln Glu Leu Glu Glu Asp Arg Ala Glu Arg Leu Thr
                 95                 100                 105
Asn
```

<210> 35
<211> 209
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1692816CD1

<400> 35

```
Met Asn Pro Ser Met Lys Gln Lys Gln Glu Glu Ile Lys Glu Asn
  1                 5                  10                  15
Ile Lys Asn Ser Ser Val Pro Arg Arg Thr Leu Lys Met Ile Gln
                 20                  25                  30
Pro Ser Ala Ser Gly Ser Leu Val Gly Arg Glu Asn Glu Leu Ser
                 35                  40                  45
Ala Gly Leu Ser Lys Arg Lys His Arg Asn Asp His Leu Thr Ser
                 50                  55                  60
Thr Thr Ser Ser Pro Gly Val Ile Val Pro Glu Ser Ser Glu Asn
                 65                  70                  75
Lys Asn Leu Gly Gly Val Thr Gln Glu Ser Phe Asp Leu Met Ile
                 80                  85                  90
Lys Glu Asn Pro Ser Ser Gln Tyr Trp Lys Glu Val Ala Glu Lys
```

```
                  95                  100                 105
Arg Arg Lys Ala Leu Tyr Glu Ala Leu Lys Glu Asn Glu Lys Leu
                 110                 115                 120
His Lys Glu Ile Glu Gln Lys Asp Asn Glu Ile Ala Arg Leu Lys
                 125                 130                 135
Lys Glu Asn Lys Glu Leu Ala Glu Val Ala Glu His Val Gln Tyr
                 140                 145                 150
Met Ala Glu Leu Ile Glu Arg Leu Asn Gly Glu Pro Leu Asp Asn
                 155                 160                 165
Phe Glu Ser Leu Asp Asn Gln Glu Phe Asp Ser Glu Glu Glu Thr
                 170                 175                 180
Val Glu Asp Ser Leu Val Glu Asp Ser Glu Ile Gly Thr Cys Ala
                 185                 190                 195
Glu Gly Thr Val Ser Ser Ser Thr Asp Ala Lys Pro Cys Ile
                 200                 205
```

<210> 36
<211> 212
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1968191CD1

<400> 36

```
Met Leu Gly Asn Glu Trp Ser Lys Leu Pro Pro Glu Glu Lys Gln
  1                5                  10                  15
Arg Tyr Leu Asp Glu Ala Asp Arg Asp Lys Glu Arg Tyr Met Lys
                 20                  25                  30
Glu Leu Glu Gln Tyr Gln Lys Thr Glu Ala Tyr Lys Val Phe Ser
                 35                  40                  45
Arg Lys Thr Gln Asp Arg Gln Lys Gly Lys Ser His Arg Gln Asp
                 50                  55                  60
Ala Ala Arg Gln Ala Thr His Asp His Glu Lys Glu Thr Glu Val
                 65                  70                  75
Lys Glu Arg Ser Val Phe Asp Ile Pro Ile Phe Thr Glu Glu Phe
                 80                  85                  90
Leu Asn His Ser Lys Ala Arg Glu Ala Glu Leu Arg Gln Leu Arg
                 95                 100                 105
Lys Ser Asn Met Glu Phe Glu Glu Arg Asn Ala Ala Leu Gln Lys
                110                 115                 120
His Val Glu Ser Met Arg Thr Ala Val Glu Lys Leu Glu Val Asp
                125                 130                 135
Val Ile Gln Glu Arg Ser Arg Asn Thr Val Leu Gln Gln His Leu
                140                 145                 150
Glu Thr Leu Arg Gln Val Leu Thr Ser Ser Phe Ala Ser Met Pro
                155                 160                 165
Leu Pro Gly Ser Gly Glu Thr Pro Thr Val Asp Thr Ile Asp Ser
                170                 175                 180
Tyr Met Asn Arg Leu His Ser Ile Ile Leu Ala Asn Pro Gln Asp
                185                 190                 195
Asn Glu Asn Phe Ile Ala Thr Val Arg Glu Val Val Asn Arg Leu
                200                 205                 210
Asp Arg
```

<210> 37
<211> 359
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2052061CD1

<400> 37

```
Met Val Asp Met Asp Lys Leu Ile Asn Asn Leu Glu Val Gln Leu
  1               5                  10                  15
Asn Ser Glu Gly Gly Ser Met Gln Val Phe Lys Gln Val Thr Ala
             20                  25                  30
Ser Val Arg Asn Arg Asp Pro Pro Glu Ile Glu Tyr Thr Ser Asn
             35                  40                  45
Met Thr Ser Pro Thr Leu Leu Asp Ala Asn Pro Met Glu Asn Pro
             50                  55                  60

Ala Leu Phe Asn Asp Ile Lys Ile Glu Pro Pro Glu Glu Leu Leu
             65                  70                  75
Ala Ser Asp Phe Ser Leu Pro Gln Val Glu Pro Val Asp Leu Ser
             80                  85                  90
Phe His Lys Pro Lys Ala Pro Leu Gln Pro Ala Ser Met Leu Gln
             95                 100                 105
Ala Pro Ile Arg Pro Pro Lys Pro Gln Ser Ser Pro Gln Thr Leu
            110                 115                 120
Val Val Ser Thr Ser Thr Ser Asp Met Ser Thr Ser Ala Asn Ile
            125                 130                 135
Pro Thr Val Leu Thr Pro Gly Ser Val Leu Thr Ser Ser Gln Ser
            140                 145                 150
Thr Gly Ser Gln Gln Ile Leu His Val Ile His Thr Ile Pro Ser
            155                 160                 165
Val Ser Leu Pro Asn Lys Met Gly Gly Leu Lys Thr Ile Pro Val
            170                 175                 180
Val Val Gln Ser Leu Pro Met Val Tyr Thr Thr Leu Pro Ala Asp
            185                 190                 195
Gly Gly Pro Ala Ala Ile Thr Val Pro Leu Ile Gly Gly Asp Gly
            200                 205                 210
Lys Asn Ala Gly Ser Val Lys Val Asp Pro Thr Ser Met Ser Pro
            215                 220                 225
Leu Glu Ile Pro Ser Asp Ser Glu Glu Ser Thr Ile Glu Ser Gly
            230                 235                 240
Ser Ser Ala Leu Gln Ser Leu Gln Gly Leu Gln Gln Glu Pro Ala
            245                 250                 255
Ala Met Ala Gln Met Gln Gly Glu Glu Ser Leu Asp Leu Lys Arg
            260                 265                 270
Arg Arg Ile His Gln Cys Asp Phe Ala Gly Cys Ser Lys Val Tyr
            275                 280                 285
Thr Lys Ser Ser His Leu Lys Ala His Arg Arg Ile His Thr Gly
            290                 295                 300
Glu Lys Pro Tyr Lys Cys Thr Trp Asp Gly Cys Ser Trp Lys Phe
            305                 310                 315
Ala Arg Ser Asp Glu Leu Thr Arg His Phe Arg Lys His Thr Gly
            320                 325                 330
Ile Lys Pro Phe Arg Cys Thr Asp Cys Asn Arg Ser Phe Ser Arg
            335                 340                 345
Ser Asp His Leu Ser Leu His Arg Arg Arg His Asp Thr Met
            350                 355
```

<210> 38
<211> 445
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2056207CD1

<400> 38
Met Val Glu Cys Ile Arg Glu Val Asn Glu Val Ile Gln Asn Pro
1 5 10 15
Ala Thr Ile Thr Arg Ile Leu Leu Ser His Phe Asn Trp Asp Lys
20 25 30
Glu Lys Leu Met Glu Arg Tyr Phe Asp Gly Asn Leu Glu Lys Leu
35 40 45
Phe Ala Glu Cys His Val Ile Asn Pro Ser Lys Lys Ser Arg Thr
50 55 60
Arg Gln Met Asn Thr Arg Ser Ser Ala Gln Asp Met Pro Cys Gln
65 70 75
Ile Cys Tyr Leu Asn Tyr Pro Asn Ser Tyr Phe Thr Gly Leu Glu
80 85 90
Cys Gly His Lys Phe Cys Met Gln Cys Trp Ser Glu Tyr Leu Thr
95 100 105
Thr Lys Ile Met Glu Glu Gly Met Gly Gln Thr Ile Ser Cys Pro
110 115 120
Ala His Gly Cys Asp Ile Leu Val Asp Asp Asn Thr Val Met Arg
125 130 135
Leu Ile Thr Asp Ser Lys Val Lys Leu Lys Tyr Gln His Leu Ile
140 145 150
Thr Asn Ser Phe Val Glu Cys Asn Arg Leu Leu Lys Trp Cys Pro
155 160 165
Ala Pro Asp Cys His His Val Val Lys Val Gln Tyr Pro Asp Ala
170 175 180
Lys Pro Val Arg Cys Lys Cys Gly Arg Gln Phe Cys Phe Asn Cys
185 190 195
Gly Glu Asn Trp His Asp Pro Val Lys Cys Lys Trp Leu Lys Lys
200 205 210
Trp Ile Lys Lys Cys Asp Asp Asp Ser Glu Thr Ser Asn Trp Ile
215 220 225
Ala Ala Asn Thr Lys Glu Cys Pro Lys Cys His Val Thr Ile Glu
230 235 240
Lys Asp Gly Gly Cys Asn His Met Val Cys Arg Asn Gln Asn Cys
245 250 255
Lys Ala Glu Phe Cys Trp Val Cys Leu Gly Pro Trp Glu Pro His
260 265 270
Gly Ser Ala Trp Tyr Asn Cys Asn Arg Tyr Asn Glu Asp Asp Ala
275 280 285
Lys Ala Ala Arg Asp Ala Gln Glu Arg Ser Arg Ala Ala Leu Gln
290 295 300
Arg Tyr Leu Phe Tyr Cys Asn Arg Tyr Met Asn His Met Gln Ser
305 310 315
Leu Arg Phe Glu His Lys Leu Tyr Ala Gln Val Lys Gln Lys Met
320 325 330
Glu Glu Met Gln Gln His Asn Met Ser Trp Ile Glu Val Gln Phe
335 340 345
Leu Lys Lys Ala Val Asp Val Leu Cys Gln Cys Arg Ala Thr Leu
350 355 360
Met Tyr Thr Tyr Val Phe Ala Phe Tyr Leu Lys Lys Asn Asn Gln
365 370 375
Ser Ile Ile Phe Glu Asn Asn Gln Ala Asp Leu Glu Asn Ala Thr
380 385 390

```
Glu Val Leu Ser Gly Tyr Leu Glu Arg Asp Ile Ser Gln Asp Ser
                395                 400                 405
Leu Gln Asp Ile Lys Gln Lys Val Gln Asp Lys Tyr Arg Tyr Cys
                410                 415                 420
Glu Ser Arg Arg Arg Val Leu Leu Gln His Val His Glu Gly Tyr
                425                 430                 435
Glu Lys Asp Leu Trp Glu Tyr Ile Glu Asp
                440                 445
```

<210> 39
<211> 433
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2101803CD1

<400> 39

```
Met Arg Ala Glu Gly Leu Gly Gly Leu Glu Arg Phe Cys Ser Pro
  1               5                  10                  15
Gly Lys Gly Arg Gly Leu Arg Ala Leu Gln Pro Phe Gln Val Gly
                20                  25                  30
Asp Leu Leu Phe Ser Cys Pro Ala Tyr Ala Tyr Val Leu Thr Val
                35                  40                  45
Asn Glu Arg Gly Asn His Cys Glu Tyr Cys Phe Thr Arg Lys Glu
                50                  55                  60
Gly Leu Ser Lys Cys Gly Arg Cys Lys Gln Ala Phe Tyr Cys Asn
                65                  70                  75
Val Glu Cys Gln Lys Glu Asp Trp Pro Met His Lys Leu Glu Cys
                80                  85                  90
Ser Pro Met Val Val Phe Gly Glu Asn Trp Asn Pro Ser Glu Thr
                95                 100                 105
Val Arg Leu Thr Ala Arg Ile Leu Ala Lys Gln Lys Ile His Pro
               110                 115                 120
Glu Arg Thr Pro Ser Glu Lys Leu Leu Ala Val Lys Glu Phe Glu
               125                 130                 135
Ser His Leu Asp Lys Leu Asp Asn Glu Lys Lys Asp Leu Ile Gln
               140                 145                 150
Ser Asp Ile Ala Ala Leu His His Phe Tyr Ser Lys His Leu Glu
               155                 160                 165
Phe Pro Asp Asn Asp Ser Leu Val Val Leu Phe Ala Gln Val Asn
               170                 175                 180
Cys Asn Gly Phe Thr Ile Glu Asp Glu Glu Leu Ser His Leu Gly
               185                 190                 195
Ser Ala Ile Phe Pro Asp Val Ala Leu Met Asn His Ser Cys Cys
               200                 205                 210
Pro Asn Val Ile Val Thr Tyr Lys Gly Thr Leu Ala Glu Val Arg
               215                 220                 225
Ala Val Gln Glu Ile Lys Pro Gly Glu Glu Val Phe Thr Ser Tyr
               230                 235                 240
Ile Asp Leu Leu Tyr Pro Thr Glu Asp Arg Asn Asp Arg Leu Arg
               245                 250                 255
Asp Ser Tyr Phe Phe Thr Cys Glu Cys Gln Glu Cys Thr Thr Lys
               260                 265                 270
Asp Lys Asp Lys Ala Lys Val Glu Ile Arg Lys Leu Ser Asp Pro
               275                 280                 285
Pro Lys Ala Glu Ala Ile Arg Asp Met Val Arg Tyr Ala Arg Asn
               290                 295                 300
```

```
Val Ile Glu Glu Phe Arg Arg Ala Lys His Tyr Lys Ser Pro Ser
                305                 310                 315
Glu Leu Leu Glu Ile Cys Glu Leu Ser Gln Glu Lys Met Ser Ser
                320                 325                 330
Val Phe Glu Asp Ser Asn Val Tyr Met Leu His Met Met Tyr Gln
                335                 340                 345
Ala Met Gly Val Cys Leu Tyr Met Gln Asp Trp Glu Gly Ala Leu
                350                 355                 360
Gln Tyr Gly Gln Lys Ile Ile Lys Pro Tyr Ser Lys His Tyr Pro
                365                 370                 375
Leu Tyr Ser Leu Asn Val Ala Ser Met Trp Leu Lys Leu Gly Arg
                380                 385                 390
Leu Tyr Met Gly Leu Glu His Lys Ala Ala Gly Glu Lys Ala Leu
                395                 400                 405
Lys Lys Ala Ile Ala Ile Met Glu Val Ala His Gly Lys Asp His
                410                 415                 420
Pro Tyr Ile Ser Glu Ile Lys Gln Glu Ile Glu Ser His
                425                 430
```

<210> 40
<211> 355
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2112362CD1

<400> 40

```
Met Ser Val Asn Tyr Ala Ala Gly Leu Ser Pro Tyr Ala Asp Lys
  1                 5                  10                  15
Gly Lys Cys Gly Leu Pro Glu Ile Phe Asp Pro Pro Glu Glu Leu
                 20                  25                  30
Glu Arg Lys Val Trp Glu Leu Ala Arg Leu Val Trp Gln Ser Ser
                 35                  40                  45
Asn Val Val Phe His Thr Gly Ala Gly Ile Ser Thr Ala Ser Gly
                 50                  55                  60
Ile Pro Asp Phe Arg Gly Pro His Gly Val Trp Thr Met Glu Glu
                 65                  70                  75
Arg Gly Leu Ala Pro Lys Phe Asp Thr Thr Phe Glu Ser Ala Arg
                 80                  85                  90
Pro Thr Gln Thr His Met Ala Leu Val Gln Leu Glu Arg Val Gly
                 95                 100                 105
Leu Leu Arg Phe Leu Val Ser Gln Asn Val Asp Gly Leu His Val
                110                 115                 120
Arg Ser Gly Phe Pro Arg Asp Lys Leu Ala Glu Leu His Gly Asn
                125                 130                 135
Met Phe Val Glu Glu Cys Ala Lys Cys Lys Thr Gln Tyr Val Arg
                140                 145                 150
Asp Thr Val Val Gly Thr Met Gly Leu Lys Ala Thr Gly Arg Leu
                155                 160                 165
Cys Thr Val Ala Lys Ala Arg Gly Leu Arg Ala Cys Arg Gly Glu
                170                 175                 180
Leu Arg Asp Thr Ile Leu Asp Trp Glu Asp Ser Leu Pro Asp Arg
                185                 190                 195
Asp Leu Ala Leu Ala Asp Glu Ala Ser Arg Asn Ala Asp Leu Ser
                200                 205                 210
Ile Thr Leu Gly Thr Ser Leu Gln Ile Arg Pro Ser Gly Asn Leu
                215                 220                 225
```

```
Pro Leu Ala Thr Lys Arg Arg Gly Gly Arg Leu Val Ile Val Asn
                230                 235                 240
Leu Gln Pro Thr Lys His Asp Arg His Ala Asp Leu Arg Ile His
                245                 250                 255
Gly Tyr Val Asp Glu Val Met Thr Arg Leu Met Lys His Leu Gly
                260                 265                 270
Leu Glu Ile Pro Ala Trp Asp Gly Pro Arg Val Leu Glu Arg Ala
                275                 280                 285
Leu Pro Pro Leu Pro Arg Pro Pro Thr Pro Lys Leu Glu Pro Lys
                290                 295                 300
Glu Glu Ser Pro Thr Arg Ile Asn Gly Ser Ile Pro Ala Gly Pro
                305                 310                 315
Lys Gln Glu Pro Cys Ala Gln His Asn Gly Ser Glu Pro Ala Ser
                320                 325                 330
Pro Lys Arg Glu Arg Pro Thr Ser Pro Ala Pro His Arg Pro Pro
                335                 340                 345
Lys Arg Val Lys Ala Lys Ala Val Pro Ser
                350                 355
```

<210> 41
<211> 443
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2117346CD1

<400> 41

```
Met Asp Arg Leu Gly Ser Phe Ser Asn Asp Pro Ser Asp Lys Pro
  1                 5                  10                  15
Pro Cys Arg Gly Cys Ser Ser Tyr Leu Met Glu Pro Tyr Ile Lys
                 20                  25                  30
Cys Ala Glu Cys Gly Pro Pro Pro Phe Phe Leu Cys Leu Gln Cys
                 35                  40                  45
Phe Thr Arg Gly Phe Glu Tyr Lys Lys His Gln Ser Asp His Thr
                 50                  55                  60
Tyr Glu Ile Met Thr Ser Asp Phe Pro Val Leu Asp Pro Ser Trp
                 65                  70                  75
Thr Ala Gln Glu Glu Met Ala Leu Leu Glu Ala Val Met Asp Cys
                 80                  85                  90
Gly Phe Gly Asn Trp Gln Asp Val Ala Asn Gln Met Cys Thr Lys
                 95                 100                 105
Thr Lys Glu Glu Cys Glu Lys His Tyr Met Lys His Phe Ile Asn
                110                 115                 120
Asn Pro Leu Phe Ala Ser Thr Leu Leu Asn Leu Lys Gln Ala Glu
                125                 130                 135
Glu Ala Lys Thr Ala Asp Thr Ala Ile Pro Phe His Ser Thr Asp
                140                 145                 150
Asp Pro Pro Arg Pro Thr Phe Asp Ser Leu Leu Ser Arg Asp Met
                155                 160                 165
Ala Gly Tyr Met Pro Ala Arg Ala Asp Phe Ile Glu Glu Phe Asp
                170                 175                 180
Asn Tyr Ala Glu Trp Asp Leu Arg Asp Ile Asp Phe Val Glu Asp
                185                 190                 195
Asp Ser Asp Ile Leu His Ala Leu Lys Met Ala Val Val Asp Ile
                200                 205                 210
Tyr His Ser Arg Leu Lys Glu Arg Gln Arg Arg Lys Lys Ile Ile
                215                 220                 225
```

```
Arg Asp His Gly Leu Ile Asn Leu Arg Lys Phe Gln Leu Met Glu
                230                 235                 240
Arg Arg Tyr Pro Lys Glu Val Gln Asp Leu Tyr Glu Thr Met Arg
                245                 250                 255
Arg Phe Ala Arg Ile Val Gly Pro Val Glu His Asp Lys Phe Ile
                260                 265                 270
Glu Ser His Ala Leu Glu Phe Glu Leu Arg Arg Glu Ile Lys Arg
                275                 280                 285
Leu Gln Glu Tyr Arg Thr Ala Gly Ile Thr Asn Phe Cys Ser Ala
                290                 295                 300
Arg Thr Tyr Asp His Leu Lys Lys Thr Arg Glu Glu Glu Arg Leu
                305                 310                 315
Lys Arg Thr Met Leu Ser Glu Val Leu Gln Tyr Ile Gln Asp Ser
                320                 325                 330
Ser Ala Cys Gln Gln Trp Leu Arg Arg Gln Ala Asp Ile Asp Ser
                335                 340                 345
Gly Leu Ser Pro Ser Ile Pro Met Ala Ser Asn Ser Gly Arg Arg
                350                 355                 360
Ser Ala Pro Pro Leu Asn Leu Thr Gly Leu Pro Gly Thr Glu Lys
                365                 370                 375
Leu Asn Glu Lys Glu Lys Glu Leu Cys Gln Met Val Arg Leu Val
                380                 385                 390
Pro Gly Ala Tyr Leu Glu Tyr Lys Ser Ala Leu Leu Asn Glu Cys
                395                 400                 405
Asn Lys Gln Gly Gly Leu Arg Leu Ala Gln Ala Arg Ala Leu Ile
                410                 415                 420
Lys Ile Asp Val Asn Lys Thr Arg Lys Ile Tyr Asp Phe Leu Ile
                425                 430                 435
Arg Glu Gly Tyr Ile Thr Lys Gly
                440
```

<210> 42
<211> 164
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2119917CD1

<400> 42

```
Met Thr Ala Ser Ala Gln Pro Arg Gly Arg Arg Pro Gly Val Gly
  1                 5                  10                  15
Val Gly Val Val Val Thr Ser Cys Lys His Pro Arg Cys Val Leu
                 20                  25                  30
Leu Gly Lys Arg Lys Gly Ser Val Gly Ala Gly Ser Phe Gln Leu
                 35                  40                  45
Pro Gly Gly His Leu Glu Phe Gly Glu Thr Trp Glu Glu Cys Ala
                 50                  55                  60
Gln Arg Glu Thr Trp Glu Glu Ala Ala Leu His Leu Lys Asn Val
                 65                  70                  75
His Phe Ala Ser Val Val Asn Ser Phe Ile Glu Lys Glu Asn Tyr
                 80                  85                  90
His Tyr Val Thr Ile Leu Met Lys Gly Glu Val Asp Val Thr His
                 95                 100                 105
Asp Ser Glu Pro Lys Asn Val Glu Pro Glu Lys Asn Glu Ser Trp
                110                 115                 120
Glu Trp Val Pro Trp Glu Glu Leu Pro Pro Leu Asp Gln Leu Phe
                125                 130                 135
```

```
Trp Gly Leu Arg Cys Leu Lys Glu Gln Gly Tyr Asp Pro Phe Lys
                140                 145                 150
Glu Asp Leu Asn His Leu Val Gly Tyr Lys Gly Asn His Leu
                155                 160
```

<210> 43
<211> 215
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2123456CD1

<400> 43

```
Met Leu Gly Ala Glu Trp Ser Lys Leu Gln Pro Thr Glu Lys Gln
  1                 5                  10                  15
Arg Tyr Leu Asp Glu Ala Glu Arg Glu Lys Gln Gln Tyr Met Lys
                 20                  25                  30
Glu Leu Arg Ala Tyr Gln Gln Ser Glu Ala Tyr Lys Met Cys Thr
                 35                  40                  45
Glu Lys Ile Gln Glu Lys Lys Ile Lys Lys Glu Asp Ser Ser Ser
                 50                  55                  60
Gly Leu Met Asn Thr Leu Leu Asn Gly His Lys Gly Gly Asp Cys
                 65                  70                  75
Asp Gly Phe Ser Thr Phe Asp Val Pro Ile Phe Thr Glu Glu Phe
                 80                  85                  90
Leu Asp Gln Asn Lys Ala Arg Glu Ala Glu Leu Arg Arg Leu Arg
                 95                 100                 105
Lys Met Asn Val Ala Phe Glu Glu Gln Asn Ala Val Leu Gln Arg
                110                 115                 120
His Thr Gln Ser Met Ser Ser Ala Arg Glu Arg Leu Glu Gln Glu
                125                 130                 135
Leu Ala Leu Glu Glu Arg Arg Thr Leu Ala Leu Gln Gln Gln Leu
                140                 145                 150
Gln Ala Val Arg Gln Ala Leu Thr Ala Ser Phe Ala Ser Leu Pro
                155                 160                 165
Val Pro Gly Thr Gly Glu Thr Pro Thr Leu Gly Thr Leu Asp Phe
                170                 175                 180
Tyr Met Ala Arg Leu His Gly Ala Ile Glu Arg Asp Pro Ala Gln
                185                 190                 195
His Glu Lys Leu Ile Val Arg Ile Lys Glu Ile Leu Ala Gln Val
                200                 205                 210
Ala Ser Glu His Leu
                215
```

<210> 44
<211> 539
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2148792CD1

<400> 44

```
Met Ala Ala Leu Phe Leu Ser Ala Pro Pro Gln Ala Glu Val Thr
 1               5                  10                  15
Phe Glu Asp Val Ala Val Tyr Leu Ser Arg Glu Glu Trp Gly Arg
            20                  25                  30
Leu Gly Pro Ala Gln Arg Gly Leu Tyr Arg Asp Val Met Leu Glu
        35                  40                  45
Thr Tyr Gly Asn Leu Val Ser Leu Gly Val Gly Pro Ala Gly Pro
    50                  55                  60
Lys Pro Gly Val Ile Ser Gln Leu Glu Arg Gly Asp Glu Pro Trp
65                  70                  75
Val Leu Asp Val Gln Gly Thr Ser Gly Lys Glu His Leu Arg Val
                80                  85                  90
Asn Ser Pro Ala Leu Gly Thr Arg Thr Glu Tyr Lys Glu Leu Thr
            95                  100                 105
Ser Gln Glu Thr Phe Gly Glu Glu Asp Pro Gln Gly Ser Glu Pro
        110                 115                 120
Val Glu Ala Cys Asp His Ile Ser Lys Ser Glu Gly Ser Leu Glu
    125                 130                 135
Lys Leu Val Glu Gln Arg Gly Pro Arg Ala Val Thr Leu Thr Asn
140                 145                 150
Gly Glu Ser Ser Arg Glu Ser Gly Gly Asn Leu Arg Leu Leu Ser
155                 160                 165
Arg Pro Val Pro Asp Gln Arg Pro His Lys Cys Asp Ile Cys Glu
                170                 175                 180
Gln Ser Phe Glu Gln Arg Ser Tyr Leu Asn Asn His Lys Arg Val
            185                 190                 195
His Arg Ser Lys Lys Thr Asn Thr Val Arg Asn Ser Gly Glu Ile
        200                 205                 210
Phe Ser Ala Asn Leu Val Val Lys Glu Asp Gln Lys Ile Pro Thr
    215                 220                 225
Gly Lys Lys Leu His Tyr Cys Ser Tyr Cys Gly Lys Thr Phe Arg
230                 235                 240
Tyr Ser Ala Asn Leu Val Lys His Gln Arg Leu His Thr Glu Glu
245                 250                 255
Lys Pro Tyr Lys Cys Asp Glu Cys Gly Lys Ala Phe Ser Gln Ser
            260                 265                 270
Cys Glu Phe Ile Asn His Arg Arg Met His Ser Gly Glu Ile Pro
        275                 280                 285
Tyr Arg Cys Asp Glu Cys Gly Lys Thr Phe Thr Arg Arg Pro Asn
    290                 295                 300
Leu Met Lys His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Lys
305                 310                 315
Cys Gly Glu Cys Gly Lys His Phe Ser Ala Tyr Ser Ser Leu Ile
                320                 325                 330
Tyr His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Lys Cys Asn
            335                 340                 345
Asp Cys Gly Lys Ala Phe Ser Asp Gly Ser Ile Leu Ile Arg His
        350                 355                 360
Arg Arg Thr His Thr Gly Glu Lys Pro Phe Glu Cys Lys Glu Cys
    365                 370                 375
Gly Lys Gly Phe Thr Gln Ser Ser Asn Leu Ile Gln His Gln Arg
380                 385                 390
Ile His Thr Gly Glu Lys Pro Tyr Lys Cys Asn Glu Cys Glu Lys
395                 400                 405
Ala Phe Ile Gln Lys Thr Lys Leu Val Glu His Gln Arg Ser His
                410                 415                 420
Thr Gly Glu Lys Pro Tyr Glu Cys Asn Asp Cys Gly Lys Val Phe
            425                 430                 435
Ser Gln Ser Thr His Leu Ile Gln His Gln Arg Ile His Thr Gly
        440                 445                 450
Glu Lys Pro Tyr Lys Cys Ser Glu Cys Gly Lys Ala Phe His Asn
455                 460                 465
```

```
Ser Ser Arg Leu Ile His His Gln Arg Leu His His Gly Glu Lys
                470                 475                 480
Pro Tyr Arg Cys Ser Asp Cys Lys Lys Ala Phe Ser Gln Ser Thr
                485                 490                 495
Tyr Leu Ile Gln His Arg Arg Ile His Thr Gly Glu Lys Pro Tyr
                500                 505                 510
Lys Cys Ser Glu Cys Gly Lys Ala Phe Arg His Ser Ser Asn Met
                515                 520                 525
Cys Gln His Gln Arg Ile His Leu Arg Glu Asp Phe Ser Met
                530                 535
```

<210> 45
<211> 182
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2751943CD1

<400> 45

```
Met Ala Arg Leu Leu Trp Leu Leu Arg Gly Leu Thr Leu Gly Thr
  1               5                  10                  15
Ala Pro Arg Arg Ala Val Arg Gly Gln Ala Gly Gly Gly Gly Pro
                20                  25                  30
Gly Thr Gly Pro Gly Leu Gly Glu Ala Gly Ser Leu Ala Thr Cys
                35                  40                  45
Glu Leu Pro Leu Ala Lys Ser Glu Trp Gln Lys Lys Leu Thr Pro
                50                  55                  60
Glu Gln Phe Tyr Val Thr Arg Glu Lys Gly Thr Glu Pro Pro Phe
                65                  70                  75
Ser Gly Ile Tyr Leu Asn Asn Lys Glu Ala Gly Met Tyr His Cys
                80                  85                  90
Val Cys Cys Asp Ser Pro Leu Phe Ser Ser Glu Lys Lys Tyr Cys
                95                 100                 105
Ser Gly Thr Gly Trp Pro Ser Phe Ser Glu Ala His Gly Thr Ser
               110                 115                 120
Gly Ser Asp Glu Ser His Thr Gly Ile Leu Arg Arg Leu Asp Thr
               125                 130                 135
Ser Leu Gly Ser Ala Arg Thr Glu Val Val Cys Lys Gln Cys Glu
               140                 145                 150
Ala His Leu Gly His Val Phe Pro Asp Gly Pro Gly Pro Asn Gly
               155                 160                 165

Gln Arg Phe Cys Ile Asn Ser Val Ala Leu Lys Phe Lys Pro Arg
               170                 175                 180
Lys His
```

<210> 46
<211> 534
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3128913CD1

<400> 46
Met Ala Val Glu Ser Gly Val Ile Ser Thr Leu Ile Pro Gln Asp
1 5 10 15
Pro Pro Glu Gln Glu Leu Ile Leu Val Lys Val Glu Asp Asn Phe
20 25 30
Ser Trp Asp Glu Lys Phe Lys Gln Asn Gly Ser Thr Gln Ser Cys
35 40 45
Gln Glu Leu Phe Arg Gln Gln Phe Arg Lys Phe Cys Tyr Gln Glu
50 55 60
Thr Pro Gly Pro Arg Glu Ala Leu Ser Arg Leu Gln Glu Leu Cys
65 70 75
Tyr Gln Trp Leu Met Pro Glu Leu His Thr Lys Glu Gln Ile Leu
80 85 90
Glu Leu Leu Val Leu Glu Gln Phe Leu Ser Ile Leu Pro Glu Glu
95 100 105
Leu Gln Ile Trp Val Gln Gln His Asn Pro Glu Ser Gly Glu Glu
110 115 120
Ala Val Thr Leu Leu Glu Asp Leu Glu Arg Glu Phe Asp Asp Pro
125 130 135
Gly Gln Gln Val Pro Ala Ser Pro Gln Gly Pro Ala Val Pro Trp
140 145 150
Lys Asp Leu Thr Cys Leu Arg Ala Ser Gln Glu Ser Thr Asp Ile
155 160 165
His Leu Gln Pro Leu Lys Thr Gln Leu Lys Ser Trp Lys Pro Cys
170 175 180
Leu Ser Pro Lys Ser Asp Cys Glu Asn Ser Glu Thr Ala Thr Lys
185 190 195
Glu Gly Ile Ser Glu Glu Lys Ser Gln Gly Leu Pro Gln Glu Pro
200 205 210
Ser Phe Arg Gly Ile Ser Glu His Glu Ser Asn Leu Val Trp Lys
215 220 225
Gln Gly Ser Ala Thr Gly Glu Lys Leu Arg Ser Pro Ser Gln Gly
230 235 240
Gly Ser Phe Ser Gln Val Ile Phe Thr Asn Lys Ser Leu Gly Lys
245 250 255
Arg Asp Leu Tyr Asp Glu Ala Glu Arg Cys Leu Ile Leu Thr Thr
260 265 270
Asp Ser Ile Met Cys Gln Lys Val Pro Pro Glu Glu Arg Pro Tyr
275 280 285
Arg Cys Asp Val Cys Gly His Ser Phe Lys Gln His Ser Ser Leu
290 295 300
Thr Gln His Gln Arg Ile His Thr Gly Glu Lys Pro Tyr Lys Cys
305 310 315
Asn Gln Cys Gly Lys Ala Phe Ser Leu Arg Ser Tyr Leu Ile Ile
320 325 330
His Gln Arg Ile His Ser Gly Glu Lys Ala Tyr Glu Cys Ser Glu
335 340 345
Cys Gly Lys Ala Phe Asn Gln Ser Ser Ala Leu Ile Arg His Arg
350 355 360
Lys Ile His Thr Gly Glu Lys Ala Cys Lys Cys Asn Glu Cys Gly
365 370 375
Lys Ala Phe Ser Gln Ser Ser Tyr Leu Ile Ile His Gln Arg Ile
380 385 390
His Thr Gly Glu Lys Pro Tyr Glu Cys Asn Glu Cys Gly Lys Thr
395 400 405
Phe Ser Gln Ser Ser Lys Leu Ile Arg His Gln Arg Ile His Thr
410 415 420
Gly Glu Arg Pro Tyr Glu Cys Asn Glu Cys Gly Lys Ala Phe Arg
425 430 435
Gln Ser Ser Glu Leu Ile Thr His Gln Arg Ile His Ser Gly Glu
440 445 450
Lys Pro Tyr Glu Cys Ser Glu Cys Gly Lys Ala Phe Ser Leu Ser

```
                455                 460                 465
Ser Asn Leu Ile Arg His Gln Arg Ile His Ser Gly Glu Glu Pro
                470                 475                 480
Tyr Gln Cys Asn Glu Cys Gly Lys Thr Phe Lys Arg Ser Ser Ala
                485                 490                 495
Leu Val Gln His Gln Arg Ile His Ser Gly Asp Glu Ala Tyr Ile
                500                 505                 510
Cys Asn Glu Cys Gly Lys Ala Phe Arg His Arg Ser Val Leu Met
                515                 520                 525

Arg His Gln Arg Val His Thr Ile Lys
                530
```

<210> 47
<211> 206
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3282941CD1

<400> 47

```
Met Ser Thr Gly Ser Val Ser Asp Pro Glu Glu Met Glu Leu Arg
  1                 5                  10                  15
Gly Leu Gln Arg Glu Tyr Pro Val Pro Ala Ser Lys Arg Pro Pro
                 20                  25                  30
Leu Arg Gly Val Glu Arg Ser Tyr Ala Ser Pro Ser Asp Asn Ser
                 35                  40                  45
Ser Ala Glu Glu Glu Asp Pro Asp Gly Glu Glu Glu Arg Cys Ala
                 50                  55                  60
Leu Gly Thr Ala Gly Ser Ala Glu Gly Cys Lys Arg Lys Arg Pro
                 65                  70                  75
Arg Val Ala Gly Gly Gly Gly Ala Gly Gly Ser Ala Gly Gly Gly
                 80                  85                  90
Gly Lys Lys Pro Leu Pro Ala Lys Gly Ser Ala Ala Glu Cys Lys
                 95                 100                 105
Gln Ser Gln Arg Asn Ala Ala Asn Ala Arg Glu Arg Ala Arg Met
                110                 115                 120
Arg Val Leu Ser Lys Ala Phe Ser Arg Leu Lys Thr Ser Leu Pro
                125                 130                 135
Trp Val Pro Pro Asp Thr Lys Leu Ser Lys Leu Asp Thr Leu Arg
                140                 145                 150
Leu Ala Ser Ser Tyr Ile Ala His Leu Arg Gln Leu Leu Gln Glu
                155                 160                 165
Asp Arg Tyr Glu Asn Gly Tyr Val His Pro Val Asn Leu Thr Trp
                170                 175                 180
Pro Phe Val Val Ser Gly Arg Pro Asp Ser Asp Thr Lys Glu Val
                185                 190                 195
Ser Ala Ala Asn Arg Leu Cys Gly Thr Thr Ala
                200                 205
```

<210> 48
<211> 172
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3286656CD1

<400> 48
Met Glu Ser Val Thr Phe Glu Asp Val Ala Val Glu Phe Ile Gln
1 5 10 15
Glu Trp Ala Leu Leu Asp Ser Ala Arg Arg Ser Leu Cys Lys Tyr
20 25 30
Arg Met Leu Asp Gln Cys Arg Thr Leu Ala Ser Arg Gly Thr Pro
35 40 45
Pro Cys Lys Pro Ser Cys Val Ser Gln Leu Gly Gln Arg Ala Glu
50 55 60
Pro Lys Ala Thr Glu Arg Gly Ile Leu Arg Ala Thr Gly Val Ala
65 70 75
Trp Glu Ser Gln Leu Lys Pro Glu Glu Leu Pro Ser Met Gln Asp
80 85 90
Leu Leu Glu Glu Ala Ser Ser Arg Asp Met Gln Met Gly Pro Gly
95 100 105
Leu Phe Leu Arg Met Gln Leu Val Pro Ser Ile Glu Glu Arg Glu
110 115 120
Thr Pro Leu Thr Arg Glu Asp Arg Pro Ala Leu Gln Glu Pro Pro
125 130 135
Trp Ser Leu Gly Cys Thr Gly Leu Lys Ala Ala Met Gln Ile Gln
140 145 150
Arg Val Val Ile Pro Val Pro Thr Leu Gly His Arg Asn Pro Trp
155 160 165
Val Ala Arg Asp Ser Ala Met
170

<210> 49
<211> 275
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3490802CD1

<400> 49
Met Gly Pro Leu Gln Phe Arg Asp Val Ala Ile Glu Phe Ser Leu
1 5 10 15
Glu Glu Trp His Cys Leu Asp Thr Ala Gln Arg Asn Leu Tyr Arg
20 25 30
Asp Val Met Leu Glu Asn Tyr Arg Asn Leu Val Phe Leu Gly Ile
35 40 45
Val Val Ser Lys Pro Asp Leu Val Thr Cys Leu Glu Gln Gly Lys
50 55 60
Lys Pro Leu Thr Met Glu Arg His Glu Met Ile Ala Lys Pro Pro
65 70 75
Val Met Ser Ser His Phe Ala Gln Asp Leu Trp Pro Glu Asn Ile
80 85 90
Gln Asn Ser Phe Gln Ile Gly Met Leu Arg Arg Tyr Glu Glu Cys
95 100 105
Arg His Asp Asn Leu Gln Leu Lys Lys Gly Cys Lys Ser Val Gly
110 115 120
Glu His Lys Val His Lys Gly Gly Tyr Asn Gly Leu Asn Gln Cys
125 130 135
Leu Thr Thr Thr Gln Lys Glu Ile Phe Gln Cys Asp Lys Tyr Gly

```
                140                 145                 150
Lys Val Phe His Lys Phe Ser Asn Ser Asn Thr Tyr Lys Thr Arg
                155                 160                 165
His Thr Gly Ile Asn Leu Phe Lys Cys Ile Ile Cys Gly Lys Ala
                170                 175                 180
Phe Lys Arg Ser Ser Thr Leu Thr Thr His Lys Lys Ile His Thr
                185                 190                 195
Gly Glu Lys Pro Tyr Lys Cys Glu Glu Cys Gly Lys Ala Phe Asn
                200                 205                 210
Gln Ser Ser Asn Leu Thr Thr His Lys Arg Ile His Thr Gly Glu
                215                 220                 225
Lys Pro Tyr Lys Cys Glu Glu Cys Gly Lys Ala Phe Asn Trp Ser
                230                 235                 240
Ser Asp Leu Asn Lys His Lys Lys Ile His Ile Glu Arg Lys Pro
                245                 250                 255
Tyr Ile Val Lys Asn Val Thr Asp Leu Leu Asn Val Pro Pro Leu
                260                 265                 270
Leu Ile Ser Ile Arg
                275
```

<210> 50
<211> 236
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3507366CD1

<400> 50

```
Met Asp Lys Arg Tyr Leu Gln Phe Asp Ile Lys Ala Phe Val Glu
  1                 5                  10                  15
Asn Asn Pro Ala Ile Lys Trp Cys Pro Thr Pro Gly Cys Asp Arg
                 20                  25                  30
Ala Val Arg Leu Thr Lys Gln Gly Ser Asn Thr Ser Gly Ser Asp
                 35                  40                  45
Thr Leu Ser Phe Pro Leu Leu Arg Ala Pro Ala Val Asp Cys Gly
                 50                  55                  60
Lys Gly His Leu Phe Cys Trp Glu Cys Leu Gly Glu Ala His Glu
                 65                  70                  75
Pro Cys Asp Cys Gln Thr Trp Lys Asn Trp Leu Gln Lys Ile Thr
                 80                  85                  90
Glu Met Lys Pro Glu Glu Leu Val Gly Val Ser Glu Ala Tyr Glu
                 95                 100                 105
Asp Ala Ala Asn Cys Leu Trp Leu Leu Thr Asn Ser Lys Pro Cys
                110                 115                 120
Ala Asn Cys Lys Ser Pro Ile Gln Lys Asn Glu Gly Cys Asn His
                125                 130                 135
Met Gln Cys Ala Lys Cys Lys Tyr Asp Phe Cys Trp Ile Cys Leu
                140                 145                 150
Glu Glu Trp Lys Lys His Ser Ser Ser Thr Gly Gly Tyr Tyr Arg
                155                 160                 165
Cys Thr Arg Tyr Glu Val Ile Gln His Val Glu Glu Gln Ser Lys
                170                 175                 180
Glu Met Thr Val Glu Ala Glu Lys Lys His Lys Arg Phe Gln Glu
                185                 190                 195
Leu Asp Arg Phe Met His Tyr Tyr Thr Arg Phe Lys Asn His Glu
                200                 205                 210
His Ser Tyr Gln Leu Glu Gln Arg Leu Leu Lys Thr Ala Lys Glu
```

```
                215                 220                 225
Lys Met Glu Gln Met Ser Arg Val Ser Lys Asn
                230                 235
```

<210> 51
<211> 214
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3573060CD1

<400> 51

```
Met Asn Leu Ser Ser Ala Ser Ser Thr Glu Glu Lys Ala Val Thr
  1               5                  10                  15
Thr Val Leu Trp Gly Cys Glu Leu Ser Gln Glu Arg Arg Thr Trp
                20                  25                  30
Thr Phe Arg Pro Gln Leu Glu Gly Lys Gln Ser Cys Arg Leu Leu
                35                  40                  45
Leu His Thr Ile Cys Leu Gly Glu Lys Ala Lys Glu Glu Met His
                50                  55                  60
Arg Val Glu Ile Leu Pro Pro Ala Asn Gln Glu Asp Lys Lys Met
                65                  70                  75

Gln Pro Val Thr Ile Ala Ser Leu Gln Ala Ser Val Leu Pro Met
                80                  85                  90
Val Ser Met Val Gly Val Gln Leu Ser Pro Pro Val Thr Phe Gln
                95                 100                 105
Leu Arg Ala Gly Ser Gly Pro Val Phe Leu Ser Gly Gln Glu Arg
               110                 115                 120
Tyr Glu Ala Ser Asp Leu Thr Trp Glu Glu Glu Glu Glu Glu Glu
               125                 130                 135
Gly Glu Glu Glu Glu Glu Glu Glu Glu Asp Asp Glu Asp Glu Asp
               140                 145                 150
Ala Asp Ile Ser Leu Glu Glu Gln Ser Pro Val Lys Gln Val Lys
               155                 160                 165
Arg Leu Val Pro Gln Lys Gln Ala Ser Val Ala Lys Lys Lys Lys
               170                 175                 180
Leu Glu Lys Glu Glu Glu Glu Ile Arg Ala Ser Val Arg Asp Lys
               185                 190                 195
Ser Pro Val Lys Lys Ala Lys Ala Thr Ala Arg Ala Lys Lys Pro
               200                 205                 210
Gly Phe Lys Lys
```

<210> 52
<211> 396
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3573661CD1

<400> 52

```
Met Asn Phe Thr Val Gly Phe Lys Pro Leu Leu Gly Asp Ala His
```

```
  1               5                  10                  15
Ser Met Asp Asn Leu Glu Lys Gln Leu Ile Cys Pro Ile Cys Leu
            20                  25                  30
Glu Met Phe Ser Lys Pro Val Val Ile Leu Pro Cys Gln His Asn
            35                  40                  45
Leu Cys Arg Lys Cys Ala Asn Asp Val Phe Gln Ala Ser Asn Pro
            50                  55                  60
Leu Trp Gln Ser Arg Gly Ser Thr Thr Val Ser Ser Gly Gly Arg
            65                  70                  75
Phe Arg Cys Pro Ser Cys Arg His Glu Val Val Leu Asp Arg His
            80                  85                  90
Gly Val Tyr Gly Leu Gln Arg Asn Val Leu Val Glu Asn Ile Ile
            95                  100                 105
Asp Ile Tyr Lys Gln Glu Ser Ser Lys Pro Leu His Ser Lys Ala
            110                 115                 120
Glu Gln His Leu Met Cys Glu Glu His Glu Glu Glu Lys Ile Asn
            125                 130                 135
Ile Tyr Cys Leu Ser Cys Glu Val Pro Thr Cys Ser Leu Cys Lys
            140                 145                 150
Val Phe Gly Ala His Lys Asp Cys Glu Val Ala Pro Leu Pro Thr
            155                 160                 165
Ile Tyr Lys Arg Gln Lys Ser Glu Leu Ser Asp Gly Ile Ala Met
            170                 175                 180
Leu Val Ala Gly Asn Asp Arg Val Gln Ala Val Ile Thr Gln Met
            185                 190                 195
Glu Glu Val Cys Gln Thr Ile Glu Asp Asn Ser Arg Arg Gln Lys
            200                 205                 210
Gln Leu Leu Asn Gln Arg Phe Glu Ser Leu Cys Ala Val Leu Glu
            215                 220                 225
Glu Arg Lys Gly Glu Leu Leu Gln Ala Leu Ala Arg Glu Gln Glu
            230                 235                 240
Glu Lys Leu Gln Arg Val Arg Gly Leu Ile Arg Gln Tyr Gly Asp
            245                 250                 255

His Leu Glu Ala Ser Ser Lys Leu Val Glu Ser Ala Ile Gln Ser
            260                 265                 270
Met Glu Glu Pro Gln Met Ala Leu Tyr Leu Gln Gln Ala Lys Glu
            275                 280                 285
Leu Ile Asn Lys Val Gly Ala Met Ser Lys Val Glu Leu Ala Gly
            290                 295                 300
Arg Pro Glu Pro Gly Tyr Glu Ser Met Glu Gln Phe Thr Val Arg
            305                 310                 315
Val Glu His Val Ala Glu Met Leu Arg Thr Ile Asp Phe Gln Pro
            320                 325                 330
Gly Ala Ser Gly Gly Gly Arg Gly Gly Gly Pro Arg Arg Lys Lys
            335                 340                 345
Arg Ala Thr Arg Gly Pro Glu Glu Lys Thr Ala Arg Met Gly Pro
            350                 355                 360
Tyr Arg Pro Leu Arg Pro Asn Pro Asp Pro Leu Leu Arg Lys Ser
            365                 370                 375
Pro Arg Arg Leu Arg Ile Ser Gly Gly Arg Asn Ser Cys Arg Lys
            380                 385                 390
Lys Thr Pro Ala Ser Phe
            395
```

<210> 53
<211> 486
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3633422CD1

<400> 53

```
Met Arg Arg Leu Val His Asp Leu Leu Pro Pro Glu Val Cys Ser
  1               5                  10                  15
Leu Leu Asn Pro Ala Ala Ile Tyr Ala Asn Asn Glu Ile Ser Leu
             20                  25                  30
Arg Asp Val Glu Val Tyr Gly Phe Asp Tyr Asp Tyr Thr Leu Ala
             35                  40                  45
Gln Tyr Ala Asp Ala Leu His Pro Glu Ile Phe Ser Thr Ala Arg
             50                  55                  60
Asp Ile Leu Ile Glu His Tyr Lys Tyr Pro Glu Gly Ile Arg Lys
             65                  70                  75
Tyr Asp Tyr Asn Pro Ser Phe Ala Ile Arg Gly Leu His Tyr Asp
             80                  85                  90
Ile Gln Lys Ser Leu Leu Met Lys Ile Asp Ala Phe His Tyr Val
             95                  100                 105
Gln Leu Gly Thr Ala Tyr Arg Gly Leu Gln Pro Val Pro Asp Glu
            110                 115                 120
Glu Val Ile Glu Leu Tyr Gly Gly Thr Gln His Ile Pro Leu Tyr
            125                 130                 135
Gln Met Ser Gly Phe Tyr Gly Lys Gly Pro Ser Ile Lys Gln Phe
            140                 145                 150
Met Asp Ile Phe Ser Leu Pro Glu Met Ala Leu Leu Ser Cys Val
            155                 160                 165
Val Asp Tyr Phe Leu Gly His Ser Leu Glu Phe Asp Gln Ala His
            170                 175                 180
Leu Tyr Lys Asp Val Thr Asp Ala Ile Arg Asp Val His Val Lys
            185                 190                 195
Gly Leu Met Tyr Gln Trp Ile Glu Gln Asp Met Glu Lys Tyr Ile
            200                 205                 210
Leu Arg Gly Asp Glu Thr Phe Ala Val Leu Ser Arg Leu Val Ala
            215                 220                 225
His Gly Lys Gln Leu Phe Leu Ile Thr Asn Ser Pro Phe Ser Phe
            230                 235                 240
Val Asp Lys Gly Met Arg His Met Val Gly Pro Asp Trp Arg Gln
            245                 250                 255
Leu Phe Asp Val Val Ile Val Gln Ala Asp Lys Pro Ser Phe Phe
            260                 265                 270
Thr Asp Arg Arg Lys Pro Phe Arg Lys Leu Asp Glu Lys Gly Ser
            275                 280                 285
Leu Gln Trp Asp Arg Ile Thr Arg Leu Glu Lys Gly Lys Ile Tyr
            290                 295                 300
Arg Gln Gly Asn Leu Phe Asp Phe Leu Arg Leu Thr Glu Trp Arg
            305                 310                 315
Gly Pro Arg Val Leu Tyr Phe Gly Asp His Leu Tyr Ser Asp Leu
            320                 325                 330
Ala Asp Leu Met Leu Arg His Gly Trp Arg Thr Gly Ala Ile Ile
            335                 340                 345
Pro Glu Leu Glu Arg Glu Ile Arg Ile Ile Asn Thr Glu Gln Tyr
            350                 355                 360
Met His Ser Leu Thr Trp Gln Gln Ala Leu Thr Gly Leu Leu Glu
            365                 370                 375
Arg Met Gln Thr Tyr Gln Asp Ala Glu Ser Arg Gln Val Leu Ala
            380                 385                 390
Ala Trp Met Lys Glu Arg Gln Glu Leu Arg Cys Ile Thr Lys Ala
            395                 400                 405
Leu Phe Asn Ala Gln Phe Gly Ser Ile Phe Arg Thr Phe His Asn
            410                 415                 420
Pro Thr Tyr Phe Ser Arg Arg Leu Val Arg Phe Ser Asp Leu Tyr
```

```
                425                 430                 435
Met Ala Ser Leu Ser Cys Leu Leu Asn Tyr Arg Val Asp Phe Thr
                440                 445                 450
Phe Tyr Pro Arg Arg Thr Pro Leu Gln His Glu Ala Pro Leu Trp
                455                 460                 465
Met Asp Gln Leu Cys Thr Gly Cys Met Lys Thr Pro Phe Leu Gly
                470                 475                 480
Asp Met Ala His Ile Arg
                485
```

<210> 54
<211> 555
<212> PRT
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3993377CD1

<400> 54

```
Met Gly Ala Glu Asp Lys Leu Pro Leu Glu Asp Ser Pro Val Ile
  1               5                  10                  15
Ala Ala Leu Asp Cys Pro Ser Leu Asn Asn Ala Thr Ala Phe Ser
                20                  25                  30
Leu Leu Ala Asp Asp Ser Gln Thr Ser Thr Ser Ile Phe Ala Ser
                35                  40                  45
Pro Thr Ser Pro Pro Val Leu Gly Glu Ser Val Leu Gln Asp Asn
                50                  55                  60
Ser Phe Asp Leu Asn Asn Gly Ser Asp Ala Glu Gln Glu Glu Met
                65                  70                  75
Glu Thr Gln Ser Ser Asp Phe Pro Pro Ser Leu Thr Gln Pro Ala
                80                  85                  90
Pro Asp Gln Ser Ser Thr Ile Gln Leu His Pro Ala Thr Ser Pro
                95                 100                 105
Ala Val Ser Pro Thr Thr Ser Pro Ala Val Ser Leu Val Val Ser
               110                 115                 120
Pro Ala Ala Ser Pro Glu Ile Ser Pro Glu Val Cys Pro Ala Ala
               125                 130                 135
Ser Thr Val Val Ser Pro Ala Val Phe Ser Val Val Ser Pro Ala
               140                 145                 150
Ser Ser Ala Val Leu Pro Ala Val Ser Leu Glu Val Pro Leu Thr
               155                 160                 165
Ala Ser Val Thr Ser Pro Lys Ala Ser Pro Val Thr Ser Pro Ala
               170                 175                 180
Ala Ala Phe Pro Thr Ala Ser Pro Ala Asn Lys Asp Val Ser Ser
               185                 190                 195
Phe Leu Glu Thr Thr Ala Asp Val Glu Glu Ile Thr Gly Glu Gly
               200                 205                 210
Leu Thr Ala Ser Gly Ser Gly Asp Val Met Arg Arg Arg Ile Ala
               215                 220                 225
Thr Pro Glu Glu Val Arg Leu Pro Leu Gln His Gly Trp Arg Arg
               230                 235                 240
Glu Val Arg Ile Lys Asn Ser Ser His Arg Trp Gln Gly Glu Thr
               245                 250                 255
Trp Tyr Tyr Gly Pro Cys Gly Lys Arg Met Lys Gln Phe Pro Glu
               260                 265                 270
Val Ile Lys Tyr Leu Ser Arg Asn Val Val His Ser Val Arg Arg
               275                 280                 285
Glu His Phe Ser Phe Ser Pro Arg Met Pro Val Gly Asp Phe Phe
```

```
                290                 295                 300
Glu Glu Arg Asp Thr Pro Glu Gly Leu Gln Trp Val Gln Leu Ser
                305                 310                 315
Ala Glu Glu Ile Pro Ser Arg Ile Gln Ala Ile Thr Gly Lys Arg
                320                 325                 330
Gly Arg Pro Arg Asn Thr Glu Lys Ala Lys Thr Lys Glu Val Pro
                335                 340                 345
Lys Val Lys Arg Gly Arg Gly Arg Pro Pro Lys Val Lys Ile Thr
                350                 355                 360
Glu Leu Leu Asn Lys Thr Asp Asn Arg Pro Leu Lys Lys Leu Glu
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Ala Gln Glu Thr Leu Asn Glu Glu Asp Lys Ala Lys Ile Ala Lys
                380                 385                 390
Ser Lys Lys Lys Met Arg Gln Lys Val Gln Arg Gly Glu Cys Gln
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Thr Thr Ile Gln Gly Gln Ala Arg Asn Lys Arg Lys Gln Glu Thr
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Lys Ser Leu Lys Gln Lys Glu Ala Lys Lys Lys Ser Lys Ala Glu
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Lys Glu Lys Gly Lys Thr Lys Gln Glu Lys Leu Lys Glu Lys Val
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Lys Arg Glu Lys Lys Glu Lys Val Lys Met Lys Glu Lys Glu Glu
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Val Thr Lys Ala Lys Pro Ala Cys Lys Ala Asp Lys Thr Leu Ala
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Thr Gln Arg Arg Leu Glu Glu Arg Gln Arg Gln Gln Met Ile Leu
                485                 490                 495
Glu Asp Met Lys Lys Pro Thr Glu Asp Met Cys Leu Thr Asp His
                500                 505                 510
Gln Pro Leu Pro Asp Phe Ser Arg Val Pro Gly Leu Thr Leu Pro
                515                 520                 525
Ser Gly Ala Phe Ser Asp Cys Leu Thr Ile Val Glu Phe Leu His
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<212> PRT
<213> Homo sapiens

<220>
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<223> Incyte ID No.: 4717936CD1

<400> 55

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Lys Met Gly Thr Gly Trp Glu Gly Phe Gln Arg Thr Leu Lys Glu
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Val Ala Tyr Ile Leu Leu Cys Cys Trp Cys Ile Lys Glu Leu Leu
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<213> Homo sapiens

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<211> 2544
<212> DNA

<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 079702CB1

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<213> Homo sapiens

<220>
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<223> Incyte ID No.: 116208CB1

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<211> 1043
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No.: 179261CB1

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<212> DNA
<213> Homo sapiens

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<211> 2255
<212> DNA
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 320087CB1

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<213> Homo sapiens

<220>
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<223> Incyte ID No.: 491271CB1

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<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 585172CB1

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<213> Homo sapiens

<220>
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<223> Incyte ID No.: 997067CB1

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<211> 1574
<212> DNA
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1443262CB1

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<211> 2197
<212> DNA
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1521648CB1

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<213> Homo sapiens

<220>
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<223> Incyte ID No.: 1685494CB1

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<213> Homo sapiens

<220>
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<223> Incyte ID No.: 1730829CB1

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<210> 70
<211> 1231
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No.: 1864641CB1

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<213> Homo sapiens

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<211> 2332
<212> DNA
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2445008CB1

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<210> 73
<211> 1936
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No.: 2572462CB1

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<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No.: 2572892CB1

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<211> 759
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No.: 2785674CB1

<400> 75

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<212> DNA
<213> Homo sapiens

<220>
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<211> 2386
<212> DNA
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 2960640CB1

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<211> 1432
<212> DNA
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3454051CB1

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<210> 79
<211> 1816
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No.: 3510640CB1

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<211> 1556
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No.: 3815083CB1

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<210> 81
<211> 1951
<212> DNA
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 3988457CB1

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<210> 82
<211> 1313
<212> DNA
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 131890CB1

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<210> 83
<211> 1197
<212> DNA
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 238642CB1

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<211> 2170
<212> DNA
<213> Homo sapiens

<220>
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<210> 85
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<212> DNA
<213> Homo sapiens

<220>
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<211> 1249
<212> DNA
<213> Homo sapiens

<220>
<221> misc-feature
<223> Incyte ID No.: 1432557CB1

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<212> DNA
<213> Homo sapiens

<220>
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<212> DNA
<213> Homo sapiens

<220>
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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<212> DNA
<213> Homo sapiens

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<211> 1997
<212> DNA
<213> Homo sapiens

<220>
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<212> DNA
<213> Homo sapiens

<220>
<221> misc-feature

<223> Incyte ID No.: 2101803CB1

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<210> 96
<211> 1951
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No.: 2117346CB1

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<212> DNA
<213> Homo sapiens

<220>

<221> misc-feature
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<211> 1581
<212> DNA
<213> Homo sapiens

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<211> 2150

<212> DNA
<213> Homo sapiens

<220>
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<211> 2196
<212> DNA
<213> Homo sapiens

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<211> 749
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> 735, 736, 741
<223> a or g or c or t, unknown, or other
<223> Incyte ID No.: 3286656CB1

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gcaacccatg ggtggccagg gattctgcca tgtagcacgt gcctgcttcc cctttgcctt 660

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<211> 1311
<212> DNA
<213> Homo sapiens

<220>
<221> unsure
<222> 1294
<223> a or g or c or t, unknown, or other
<223> Incyte ID No.: 3490802CB1

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<211> 990
<212> DNA
<213> Homo sapiens

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<211> 1048
<212> DNA
<213> Homo sapiens

<220>
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<223> Incyte ID No.: 3573060CB1

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<211> 1349
<212> DNA
<213> Homo sapiens

<220>
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<211> 1642
<212> DNA
<213> Homo sapiens

<220>
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<210> 109
<211> 1818
<212> DNA
<213> Homo sapiens

<220>
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